ENDOCRINOLOGY

THE BULLETIN OF
THE ASSOCIATION FOR THE STUDY
OF INTERNAL SECRETIONS

VOLUME 20 NOVEMBER, 1936 NUMBER 6

THE HUMAN CORPUS LUTEUM AND PROGESTIN, STUDIES II[1]

J. P. PRATT, E. C. HAMBLEN, O. KAMM AND D. A. McGINTY
From the Henry Ford Hospital and the Laboratories of Parke, Davis and Company
DETROIT, MICHIGAN
and the Department of Obstetrics and Gynecology, Duke University
DURHAM, NORTH CAROLINA

The assumption that the human corpus luteum elaborates progestin rests almost entirely upon indirect evidence since it is based on experimental work on laboratory animals. Clauberg and his co-workers (1) inferred from inconclusive histological data on the uterus of a rabbit which received the extract from 55 gm. of human material that progestin is present and that the extract from 70 gm. of such tissue might cause a true progestational reaction.

The amount of progestational hormone in the corpora lutea and ovaries of different species seems to vary greatly from relatively large amounts in hog and beef ovaries to meager concentrations in sheep ovaries and the human corpus luteum. Furthermore, the progestin requirements during pregnancy as judged by the continuation of pregnancy after ovariectomy seems to vary widely. Allen and Corner (2) have shown that to prevent abortion, the pregnant castrate rabbit needs 1 Rb.U. per day. In the human, the corpus luteum or the whole ovary may be removed very early in pregnancy without occurrence of abortion. These observations do not prove, however, that progestin is dispensable during implantation of the ovum nor indeed at any time in pregnancy, since other tissues may form the hormone. Human placentas have been shown to contain progestin.

These and other theoretical considerations have prompted us to reinvestigate the problem of progestin content of human corpora lutea and to determine its concentration there in a quantitative manner. The collection of human material was begun in 1933. Three lots of material have been collected, extracted and assayed.

[1] Read before the Twentieth Annual Meeting of the Association for the Study of Internal Secretions, Kansas City, Mo., May 11, 1936.

The negative tests for progestin in the first lot of human corpora lutea were reported in 1934 (3). Inasmuch as only 40 gm. of tissue were used, the negative results of that test are now known to be due to inadequate material. The fact that a positive test was obtained from 60 gm. of tissue was mentioned in 1935 (4). Since the test rabbit which received 60 gm. died shortly after the last injection, the results were considered inconclusive. Report of details was reserved therefore, until a more satisfactory assay could be obtained. The third lot obtained during 1935 gave a strongly positive reaction with 100 gm. of tissue. The results obtained from all 3 collections are combined in table 1.

The term progestin has been retained here because no attempt was made to crystallize the extract. Progesterone implies a material that can be crystallized and therefore identified chemically. To obtain a sufficient number of human corpora lutea to provide crystals for study seems practically prohibitive, not only because of the low concentration of hormone but also because of difficulty in collection of the tissue itself.

MATERIAL

Fresh specimens of human corpora lutea obtained at the operating table were placed immediately in 95 per cent alcohol in a glass stoppered bottle. Care was taken to have as little air space above the alcohol as possible. The material was kept at room temperature throughout the period of collection. Tests of the fluid at the time of extraction demonstrated that there was no development of alkalinity which would cause deterioration of the hormone as has been shown to be possible in other experiments.

Division of the material into age groups would have been desirable but the scarcity of satisfactory material prevented this. The majority of the specimens were taken from patients more than 30 years of age. All individuals were, however, in the active reproductive age as indicated by the menstrual cycles. A few specimens from early pregnancy were also included. Besides the physiologic activity as evidence of normalcy of the corpora, all specimens as well as the ovaries from which they were removed, were examined grossly. Microscopic sections were not made in order to preserve as much tissue as possible for the test. The corpora lutea were carefully enucleated from the ovaries thereby excluding extraneous material.

The manner of preserving, the method of extraction and assay of the human corpora lutea were paralled with hog corpora, which have been used generally in progestin experiments. Under these circumstances, the hog corpora gave the average yield of 1 Rb.U. to 15 gm. of tissue.

EXTRACTION

The extraction of the material collected in 1933 has already been reported in detail (3). This lot consisted of approximately 50 corpora lutea, the corrected fresh weight of which was 131 gm.; the lot accumulated during 1934 consisted of 58 corpora lutea possessing a corrected fresh weight of 150 gm.; the accumulation of 1935 corresponded to 47 corpora equivalent to 120 gm. of fresh tissue.

Since the above material was collected and preserved in alcohol, the actual

weights did not represent the true weight of fresh tissue. In order to determine that, fresh hog corpora were similarly treated with 95 per cent alcohol and the weights determined before and after treatment. The results thus obtained permitted an approximate calculation of the fresh weight of the human tissue. It should be explained that the alcohol solutions in which the glands had been preserved were evaporated in each case and any extractive material contained therein incorporated with the subsequent extracts of the glands.

The actual process of extraction and subsequent purification of the extracts were carried out according to the methods of Allen (5) and of Allen and Meyer (6), the estrogenic hormone being removed in the last step. The

TABLE 1

Rabbit No.	Weight	Equivalent Fresh Corpus Luteum	Progestational Uterine Response
	gm.	gm.	
1	1040	10	Neg.
2	980	20	Neg.
3	1400	40	Neg.
4	1200	60*	+2
5	1170	70	+1
6	980	100	+4

* This rabbit died during the night following the 3rd day of injection of hormone.
A part of the first lot already reported is excluded from this table because theelin was not removed from the material before the assay.

final oily material was diluted with an appropriate quantity of peanut oil, so that the quantity injected daily never exceeded 0.25 cc.

ASSAYS

Assays were carried out according to the McPhail (7) modification of the Clauberg method on juvenile 1000-1200 gm. rabbits. The hormone was administered intramuscularly in oil solution once daily for 5 days subsequent to a previous administration of 150 I.U. of theelin over a period of 6 days, this being given intramuscularly in oil every other day. The animals were killed on the day following the last progestin injection. Four uterine specimens from different regions were fixed and sectioned. The average reaction of the 4 was recorded according to the McPhail scale upon which a maximal reaction is designated as +4. The results are given in table 1 which summarizes the results obtained with the 3 lots of corpora lutea referred to above.

DISCUSSION

For the study reported here, 300 gm. of fresh human corpora lutea were available. Because of the low hormone content it was necessary to use doses of extract equivalent to large amounts of tissue and to limit the number of animals used to 6. The results obtained, however, indicate that the human corpus luteum contains progestin although the equivalent of 60-100 gm. of fresh tissue is necessary to obtain definite progestational responses in the rabbit. This is in contrast to the uniformly positive results with the hog ovaries from which extracts equivalent to 15 gm. of fresh corpora lutea will cause positive

progestational reactions in the juvenile rabbit. A pair of mature hog ovaries contains in the order of magnitude 20 to 30 times as much progestin as the human ovary. According to these determinations, it takes nearly 40 human corpora lutea to yield 1 Rb.U. of progestin.

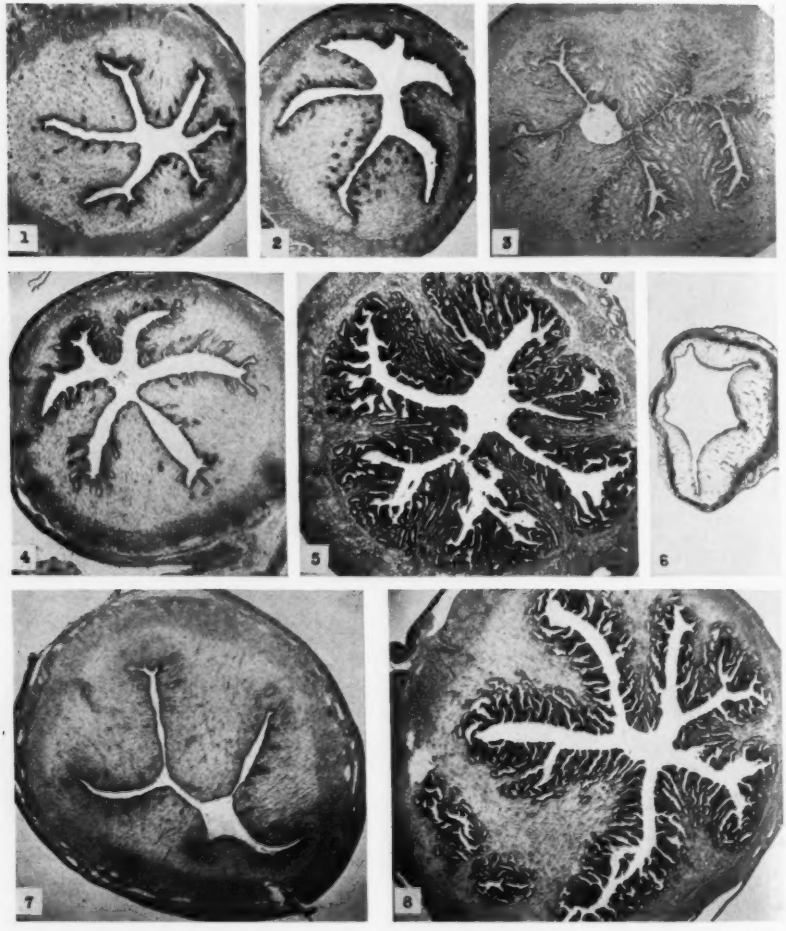


Fig. 1-8. Photomicrographs of rabbit uterii, showing responses to extract of corpus luteum, and controls. 1, Response to extract corresponding to 10 gm. fresh, human corpus luteum. 2, Extract corresponding to 18 gm. fresh corpus luteum. 3, Extract corresponding to 6 gm. fresh, human corpus luteum (3-day test only, explanation in text). 4, Extract corresponding to 70 gm. fresh, human corpus luteum. 5, Extract corresponding to 100 gm. fresh, human corpus luteum. 6, Normal uterus of immature rabbit. 7, Control rabbit uterus sensitized by 7-day theelin treatment. 8, Control rabbit uterus showing positive response to an extract corresponding to 15 gm. of hog corpus luteum.

The human placenta also contains progestin. Ehrhardt (8) and McGinty (9) have demonstrated 7 Rb.U. of progestin in a single human placenta at term. Whether this hormone is elaborated by the placenta or only stored there has not yet been determined. The relatively low yield of progestin in the human

ovary may be compensated during pregnancy by the activity of the placenta. Furthermore, it is a possibility that the placenta may compensate for the loss of corpus luteum or the whole ovary during pregnancy.

The relatively low yield of progestin from human material should not be attributed to deterioration on account of the length of time taken for accumulation of the material because the treatment of the human issue was paralleled by hog corpora lutea. It is probable, however, that the animal material came from a comparatively earlier period in the reproductive life. There is no evidence available to indicate whether the yield of progestin varies with the age. Perhaps the low content of progestin in the human indicates a greater sensitivity and therefore a small amount of the hormone is relatively more effective in this species. Perhaps the progestin may not be stored long in the corpus luteum but may be taken into the circulation as soon as elaborated. The amount found in the tissue assay, therefore, may not be a good indicator of the physiologic activity of the corpus luteum. The negative tests for progestin (10) in 500 cc. of human pregnancy blood failed to demonstrate any great concentration of progestin in the circulation.

There is a species variation in the relative need of the presence of the corpus luteum for nidation of the ovum. In the human, the need is relatively low and parallels the yield of progestin. Indications for the therapeutic use of progestin for the treatment of abortion, therefore, are theoretically speculative.

SUMMARY

Human corpora lutea removed at operation and preserved while fresh in 95 per cent alcohol were extracted by the Allen and Meyer method for progestin and assayed by the McPhail modification of the Clauberg method. Positive reactions were obtained from 60-100 gm. of fresh tissue using a single test rabbit for each level of tissue tested. About 40 human corpora lutea yielded 1 Rb.U. of progestin.

REFERENCES

1. Clauberg, C., H. W. Thiel and R. Ziecker: Arch. f. Gynäk. **152:** 61. 1933.
2. Allen, W. M. and G. W. Corner: Proc. Soc. Exper. Biol. & Med. **27:** 403. 1930.
3. Pratt, J. P.: Endocrinology **18:** 667. 1934.
4. Pratt, J. P.: Arch. Path. **19:** 380. 1935.
5. Allen, W. M.: J. Biol. Chem. **98:** 591. 1932.
6. Allen, W. M. and R. K. Meyer: Am. J. Physiol. **106:** 55. 1933.
7. McPhail, M. K.: J. Physiol. **83:** 145. 1934.
8. Ehrhardt, K.: München. med. Wchnschr. **81:** 869. 1934.
9. McGinty, D. A., N. B. McCullough and J. G. Wolter: Proc. Soc. Exper. Biol. & Med. **34:** 176. 1936.
10. Bloch, P. W.: Endocrinology **20:** 307. 1936.

THE EFFECT OF ESTROGENIC SUBSTANCES UPON THE PITUITARY, ADRENALS AND OVARIES[1]

EUGENE T. ELLISON AND JOHN C. BURCH
From the Department of Obstetrics and Gynecology, Vanderbilt University Medical School,
NASHVILLE, TENNESSEE

Although there is abundant experimental evidence that the estrogenic hormones exert an influence upon the pituitary, the nature and extent of this influence is not entirely clear. The working hypothesis that gonadal hormones suppress the pituitary, making available to the organism a reduced amount of gonad-stimulating secretion was advanced by Moore and Price (1) in 1930. They felt that results obtained by them in a large number of careful experiments, as well as certain observations of other investigators, could be explained on such a basis. In support of this concept is the work of Meyer, Leonard, Hisaw and Martin, who reported that long-continued injections of estrin resulted in a decreased ovarian-stimulating capacity of the pituitary of the adult rat (2) and in an ovarian depression in the immature animal (3). The latter observation was confirmed by Spencer, Gustavson and D'Amour (4) and by Doisy, Curtis and Collier (5). Kunde, D'Amour, Gustavson and Carlson (6) found a reduction in the size of pituitary and ovaries following prolonged estrin injections in immature dogs. It should be noted, however, that these animals showed a pronounced hyperplasia of the thyroid.

Previous to the publication of the above results, an effort to investigate the effect of estrin on the pituitary had been made in this laboratory by Burch and Cunningham (7). The only estrogenic preparation available to us at that time was a commercial alcoholic extract of human placenta[2] containing a high percentage of estrin. Castrate rats injected over a short period of time with large doses of this extract showed a marked increase in the ovarian-sitmulating capacity of the anterior pituitary.

When other workers who had used different estrogenic preparations reported opposite results, it became apparent that further work was in order. Accordingly, a second series of experiments was undertaken (8). In this series, the estrin was removed from an alcoholic extract of human placenta; the ether extract and the residuum were then compared with respect to their effects upon the ovarian-stimulating capacity of the anterior pituitaries of castrate rats. It was found that the ether extract produced a mild depression whereas the residuum produced a marked increase.

In 1933 the investigation was continued in this laboratory by Leiby (9, 10) who investigated the effects of crystalline theelin and theelol, used separately and in

[1] Read before the Twentieth Annual Meeting of the Association for the Study of Internal Secretions, Kansas City, Missouri, May 11, 1936.
[2] The extract used was Estrogen, a product of Parke, Davis & Co.

combination with the anterior-pituitary-like substance from urine of pregnant women. Striking and important results were obtained, especially with theelol. Castrate rats were injected with 200 R.U. of theelin or theelol daily for 6 days. Those receiving theelin showed hypertrophy of the pituitary only, while those receiving theelol showed a definite hypertrophy of pituitary, thyroid and adrenals.

When a daily dosage of 400 R.U. of theelol was used (unpublished data), the results were even more marked. The enlarged pituitaries of these animals showed a normal ovarian-stimulating capacity. From these results, the following inferences might be drawn. The unchanged ovarian-stimulating capacity indicated simultaneous production and release of the anterior pituitary gonadotropic substances. The increased weights of thyroid and adrenals were associated with pituitary secretion. For demonstrating pituitary function, the weights of pituitary, adrenals and thyroid serve as more adequate criteria than does the ovarian-stimulating capacity of the transplanted gland.

Subsequent work of other investigators lends possible support to the above inferences. Hohlweg (11) and Wolfe (12) have reported that injection of comparatively large amounts of Progynon-B induced marked hypertrophy of the pituitaries of normal rats. The ovaries of such animals were found to contain large corpora lutea, comparable in size and morphology to those found in pregnant rats. Subsequently, Selye, Collip and Thomson (13) and Nelson (14) obtained hypertrophy of pituitary, ovaries and adrenals in intact rats following treatment with estrone. They further demonstrated that the reactions do not take place in hypophysectomized animals. Andersen (15) reported that after castration, there is atrophy of the pituitary, adrenals and thyroid in rats. Using amniotin, she was able to restore such atrophied glands to the weights characteristic of estrus in the normal animal. Richter (16) obtained somewhat similar results in rats with pregnancy urine by mouth. Cramer and Horning (17) reported degenerative changes in the adrenals of normal and castrate female mice following long term external application of α folliculin or of ketohydroxyestrin. It should be mentioned that Leonard, Meyer and Hisaw (3) had reported in 1931 that there was an insignificant increase in the weights of pituitary, thyroid and adrenals in immature rats injected with amniotin.

Results obtained by Lane (18) indicate that estrin may have both a depressing and a stimulating effect on the pituitary. This investigator found that ovaries of immature rats injected with amniotin showed evidence of follicle stimulation in short term experiments and evidence of luteinization in long term experiments. The conclusion was drawn that estrin stimulates the secretion of the anterior pituitary follicle-stimulating factor up to a certain point, then inhibits formation and liberation of this principle, while continuing to stimulate elaboration and release of the luteinizing factor. The conclusion was further supported by results obtained when the pituitaries of the injected animals were transplanted.

Since certain changes occurring in ovaries, thyroid and adrenals as a result of estrin administration indicate stimulation of these glands, and since such changes are dependent upon the presence of the pituitary, it seems evident that the effect of estrin, at least under certain conditions, is to make available to the organism an increased amount of pituitary secretion. On the other hand, there is some evidence that estrin may depress the pituitary. In view of the variations in experimental procedures followed and chemical preparations used by the workers in this field, it seems possible that such widely divergent effects may be in part referable to differences in physiologic action of the various

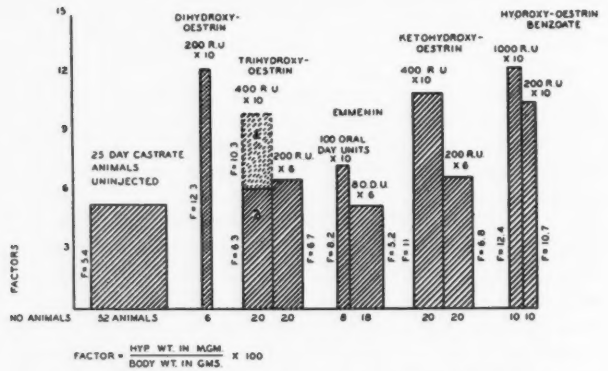


Chart I. Effect of various estrogenic substances on the weight of the pituitary of the castrate rat. Interrupted cross-hatching indicates previous experiments included here.

chemical forms of estrin and/or to differences in dosage and period of administration. This possibility suggested the present study, in which the following points have been investigated: *a)* the effects of different estrogenic substances upon the pituitary, ovaries, adrenals and thyroid of normal, castrate and hypophysectomized rats; *b)* the influence of dosage upon these effects.

MATERIAL AND METHODS

The following estrogenic substances[3] were used: trihydroxyestrin, dihydroxyestrin, ketohydroxyestrin, hydroxyestrin benzoate and the placental factor, emmenin. In the case of each substance, adult female rats were injected

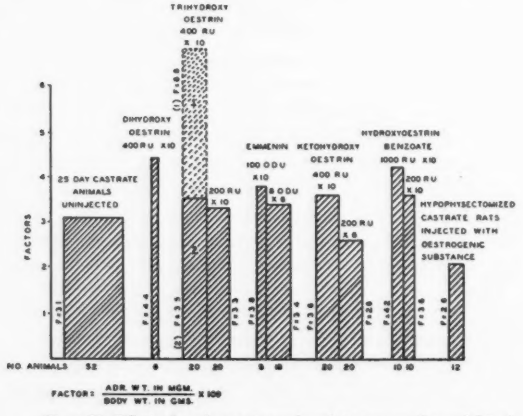

TRIHYDROXY OESTRIN 400 R.U X 10
DIHYDROXY OESTRIN 400 R.U X 10
EMMENIN 100 O.D.U X 10
KETOHYDROXY OESTRIN 400 R.U X 10
HYDROXYOESTRIN BENZOATE 1000 R.U X 10
200 R.U X 10
200 R.U X 6
80 O.D.U X 6
25 DAY CASTRATE ANIMALS UNINJECTED
HYPOPHYSECTOMIZED CASTRATE RATS INJECTED WITH OESTROGENIC SUBSTANCE
FACTORS
NO. ANIMALS
FACTOR = ADR. WT. IN MGM. / BODY WT. IN GMS. X 100

Chart II. Effect of various estrogenic substances on the weight of the adrenals of castrate rats and hypophysectomized rats. Interrupted cross-hatching indicates previous experiments included here.

[3] Trihydroxyestrin and ketohydroxyestrin, in specially prepared concentrated form, were kindly furnished by Parke, Davis & Co. through the courtesy of Mr. H. C. Fritsch. Half of the concentrated hydroxyestrin-benzoate was furnished gratuitiously by the Schering Corporation through the courtesy of Dr. Erwin Schwenk. A specially prepared emmenin concentrate was furnished gratuitously by Ayerst, McKenna and Harrison through the courtesy of Mr. Stanley Cook and Mr. Joseph Hutchinson.

daily for 10 days with moderate[4] or with relatively large amounts. The latter dose was determined as follows: each substance was used in the most concentrated solution that we were able to obtain and the largest amount that could be absorbed was given at each injection. Animals receiving moderate doses had been castrated 25 days previously. Large doses were given to 25-day castrates, to intact animals and to hypophysectomized animals. At the end of the injection period, the animals were sacrificed and the pituitaries, ovaries, adrenals and thyroids were weighed[5] and studied histologically. In each instance the glands were compared with those from a comparable number of normal, castrate and hypophysectomized controls.

RESULTS

The results are shown graphically in Charts I, II, and III. The various estrogenic preparations were found to differ markedly in potency but all produced similar effects. With respect to all of them, the bearing of dosage upon results was extremely important. Thus, animals receiving moderate amounts of hormone showed a slight but unmistakable hypertrophy of the pituitary.

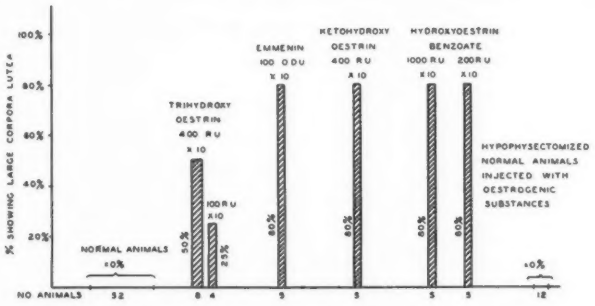


Chart III. Effect of various estrogenic substances on the ovaries of normal and hypophysectomized rats.

The weights of thyroid and adrenals were slightly above those of the controls; the increase, however, was not sufficiently marked to be of significance. When, on the other hand, large doses were used, adrenals as well as pituitary, were significantly increased in weight. Results in castrates and non-castrates were qualitatively similar. In the latter animals there was also a marked increase in weight of the ovaries.

The histological changes in the pituitary were not studied in great detail. They were in every way similar to those obtained by Wolfe (12) after the administration of large amounts of hydroxyestrin benzoate. The increased weight of the ovaries was due to the presence of large corpora lutea, which, in the majority of instances, were comparable in size and morphology to those found in normal pregnancy (fig. 1). The adrenals of the castrate animals injected with large amounts of estrogenic substances showed striking histological changes. When these glands were compared with those of the 25-day castrate

[4] In a few instances, injections of moderate amounts of trihydroxyestrin and emmenin were continued for only 6 days.

[5] Organs were weighed on a Hartmann-Braun torsion balance accurate to 0.5 mg.

controls, it was seen that there was a marked widening of the cortex. This was 1.5 to 2 times the width of the cortex of the regressive glands in the castrate uninjected group (fig. 2) and, in many instances, wider than the cortex of non-castrate controls. The zonae fasciculatis and reticularis were markedly increased in width and contained hypertrophied cellular elements and dilated sinusoids. The cells of these layers contained a finely vacuolated cytoplasm which stained homogeneously. These cells were in marked contrast to the corresponding cells in glands of uninjected castrates and intact controls. In the latter 2 groups of animals, the cells of the zona fasciculatis contained larger vacuoles but the cells of both layers were smaller and less regularly arranged. The most striking observation was the presence of relatively numerous mitoses

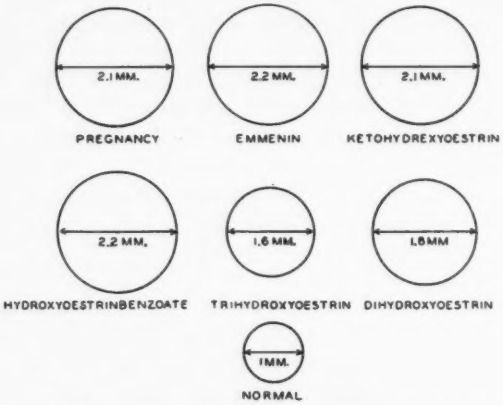


Fig. 1. Diagrammatic representation of comparative size of corpora lutea in ovaries from non-pregnant rats, pregnant rats and rats injected with various estrogenic substances. Drawn to scale from camera lucida drawings.

in the injected animals. These mitoses were found in the zona glomerulosa and the outer portion of the zona fasciculatis. In the adrenals of intact and castrate controls, mitoses were extremely rare. The histological changes in the adrenals of non-castrate injected animals were similar to those found in injected castrates.

No effects upon the glands in question were obtained in hypophysectomized animals with any of the estrogenic substances. In these animals the adrenal cortex was extremely thin and no mitoses were observed.

In all instances, the effect upon the pituitary was most marked, however, the changes in ovaries and adrenals were equally consistent and almost as striking. Some evidence of an effect upon the thyroid was obtained but since results with respect to this gland were less consistent, they have not been described.

DISCUSSION

It is obvious from these results that, under the conditions described, the various estrogenic substances, although differing markedly in potency, act similarly in causing hypertrophy of the pituitary, ovaries and adrenals. The nega-

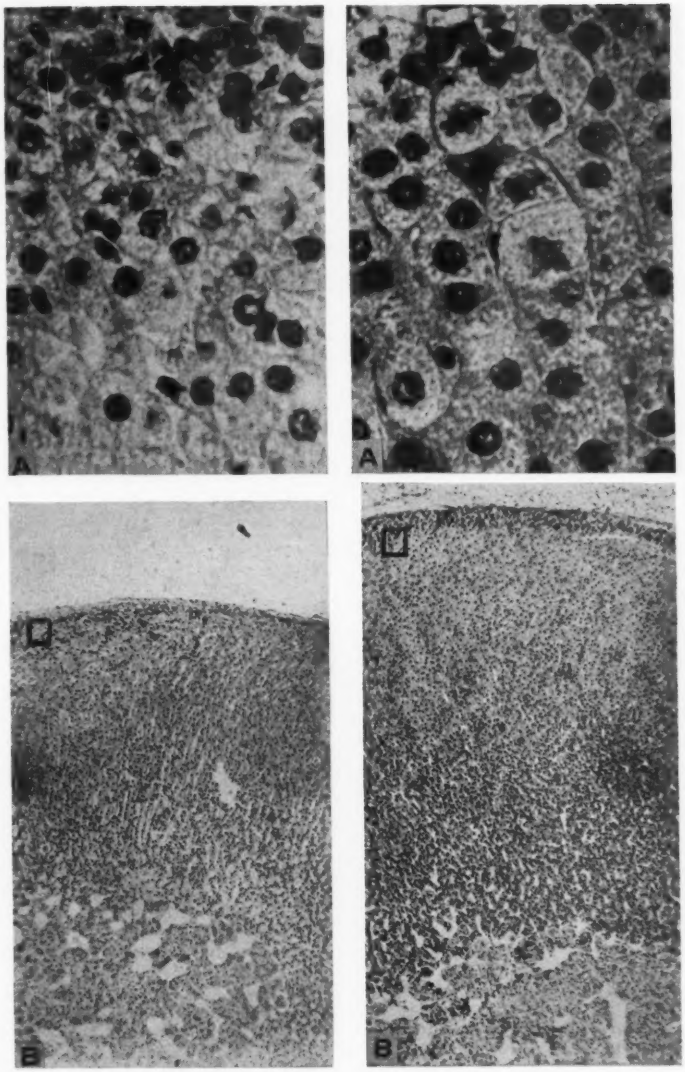


Fig. 2. Photomicrographs of the adrenal cortex of the rat. Left B, adrenal cortex of a 25-day castrate rat, x 43. Left A, a higher magnification of an area similar to that indicated by insert on left B, x 640. Right B, a typical picture of the adrenal cortex of a 25-day castrate rate produced by injection of any one of the estrogenic substances tested, x 43. Right A, higher magnification taken from area similar to the corresponding insert on right B x 640 (field chosen shows mitoses which are frequently observed in this area).

tive results following ablation of the pituitary indicate that the presence of this gland is necessary for the action of oestrin on ovaries and adrenals. Hypertrophy of and storage of secretion by the pituitary following oöphorectomy have been attributed to withdrawal of the depressing effect of estrin. On the other hand, atrophy of the adrenals and thyroid occurring as a result of long-

term castration can be repaired by the injection of estrin (Andersen, 15). Since the atrophy of these glands resulting from hypophysectomy cannot be similarly repaired, it must be assumed that the effect of estrin on the adrenal in the castrate is due to a release of the stored hypophyseal secretion. This action in the castrate and the results obtained in the present experiments must indicate that oestrin stimulates the pituitary in some manner.

We believe that our observations add evidence that the various estrogenic substances are essentially similar in their action on the body mechanisms. The differences observed are, we believe, due to little understood factors of absorption, storage, metabolism and excretion and not to differences in physiologic effects of the substances themselves.

SUMMARY

A comparison has been made of the effects of trihydroxyestrin, dihydroxyestrin, ketohydroxyestrin, hydroxyestrin benzoate and the placental estrogenic substance, emmenin, upon the pituitary, ovaries and adrenals of castrate, non-castrate and hypophysectomized rats. Injections of moderate and of large amounts of each substance were given daily for 10 days. The pituitaries, ovaries and adrenals were weighed and studied histologically, and were compared with glands from suitable control animals.

Trihydroxyestrin, dihydroxyestrin, ketohydroxyestrin, hydroxyestrin benzoate and the placental estrogenic substance emmenin, when injected in sufficient amounts, cause hypertrophy of the pituitary and adrenal glands of the castrate rat. The same substances in sufficient amounts cause hypertrophy of pituitary, adrenals and ovaries in the normal rat. The increase in size of the ovary is due solely to the formation of corpora lutea comparable in size and morphology to those found in normal pregnancy.

The effects of these substances upon the ovaries and adrenals are dependent upon the presence of the pituitary.

REFERENCES

1. Moore, C. R., and Dorothy Price: Proc. Soc. Exper. Biol. & Med. **28:** 38. 1930.
2. Meyer, R. K., S. L. Leonard, F. L. Hisaw, and S. J. Martin: Proc. Soc. Exper. Biol. & Med. **27:** 702. 1930.
3. Leonard, S. L., R. K. Meyer, and F. L. Hisaw: Endocrinology **15:** 17. 1931.
4. Spencer, J., R. G. Gustavson and F. E. D'Amour: Proc. Soc. Exper. Biol. & Med. **28:** 500. 1931.
5. Doisy, E. A., J. Curtis, and W. D. Collier: Proc. Soc. Exper. Biol. & Med. **28:** 885. 1931.
6. Kunde, M. M., F. E. D'Amour, R. G. Gustavson, and A. J. Carlson: Proc. Soc. Exper. Biol. & Med. **28:** 122. 1930.
7. Burch, John C., and R. S. Cunningham: Proc. Soc. Exper. Biol. & Med. **27:** 331. 1930.
8. Klingler, Harold, J. C. Burch, and R. S. Cunningham: Surg. Gynec. & Obst. **56:** 137. 1933.
9. Leiby, G. M.: Proc. Soc. Exper. Biol. & Med. **31:** 15. 1933.
10. Leiby, G. M.: Proc. Soc. Exper. Biol. & Med. **31:** 17. 1933.
11. Hohlweg, W.: Klin. Wchnschr. **13:** 92. 1934.
12. Wolfe, J. M.: Proc. Soc. Exper. Biol. & Med. **32:** 1192. 1935.
13. Selye, H., J. B. Collip, and D. L. Thomson: Proc. Soc. Exper. Biol. & Med. **32:** 1377. 1935.
14. Nelson, W. O.: Anat. Rec. **64:** (Suppl. p. 52.) 1936.
15. Andersen, Dorothy: J. Physiol. **83:** 15. 1934.
16. Richter, C. P.: Am. J. Physiol. **110:** 499. 1935.
17. Cramer, W., and E. S. Horning: Lancet **1:** 247. 1936.
18. Lane, C. E.: Am. J. Physiol. **110:** 681. 1935.

THE TIME ELEMENT IN THE PITUITARY-OVARIAN RESPONSE TO LARGE DOSES OF THE ESTROGENIC HORMONE[1]

CHARLES MAZER, S. LEON ISRAEL AND BERNARD J. ALPERS
From the Department of Gynecology, Mount Sinai Hospital, and the Laboratory of Neurosurgery, Hospital of the University of Pennsylvania
PHILADELPHIA, PENNSYLVANIA

Following the lucid demonstration of the dependency of the gonads upon the anterior hypophysis (1, 2), it has also been shown that, at a given height of concentration, gonad hormones of either sex suppress the activity of the anterior hypophysis (3, 4, 5, 6). This, in turn, causes regressive changes in the gonads (3, 4, 7, 8, 9, 10).

However, Hohlweg's more recent observations (11) on the pituitary-ovarian response to massive doses of estrogenic substance in both adult and infantile rodents indicated the existence of a hitherto unsuspected reciprocal relationship between gonad hormones and the anterior hypophysis. Most remarkable was his demonstration of premature development of corpora lutea in the ovaries of infantile rats given 500 R.U. of hydroxyestrin benzoate as a single dose. The concomitant changes observed by Hohlweg in the anterior hypophyses of the rodents included alterations of the chief cells and a slight increase of the eosinophile cells. The possible mediation of a hypothetical sex center (12), acting as a regulatory buffer for the anterior hypophysis, is interesting but irrelevant—the relationship between the anterior hypophysis and the gonads remains the same.

The present study was undertaken in order to observe further the phenomena reported by Hohlweg. The test animals were rats and isolated rabbits, both infantile and adult. The estrogenic substances employed included ketohydroxyestrin (theelin), hydroxyestrin benzoate (progynon-B) and dihydroxyestrin (progynon-D). They were administered hypodermically, daily in oily solution for either 7 or from 21 to 30 days. The results observed were the same irrespective of the kind of estrogenic substance employed. For purposes of orientation, a series of infantile rats, weighing 35 to 40 gm., were given single injections of 500 R.U. of estrogenic substance and their ovaries removed 7 days later (Hohlweg's original experiment). The major experiments, performed on both infantile and adult rats and rabbits, are divisible into 2 groups, depending on the duration of estrogenic-substance administration. The ovaries and anterior hypophyses were weighed (table 1) and histologically studied in comparison with those of control animals of the same strain in each instance. The thyroid glands and adrenals were also studied in some of the experiments.

[1] Read before the Twentieth Annual Meeting of the Association for the Study of Internal Secretions, Kansas City, Mo., May 11, 1936.

Effects of a single, large dose of estrogenic substance on the ovaries of infantile rats.

Five of 10 infantile (35-40 gm.) rats were each given a single injection of 500 R.U. of estrogenic substance; the remaining 5 animals served as controls. The animals were killed and their ovaries examined 1 week following the administration of estrogenic substance. Grossly, the ovaries of the treated animals were larger and definitely more vascular than those of the control animals. The average weight of both ovaries of the control animals was 15 mg. and of the treated animals 21.5 mg. Microscopically, the ovaries of all the treated animals showed advanced follicular growth. Corpora lutea were found in 3 of the 5 treated rodents (fig. 1). Concluding that these findings were sufficiently corroborative of Hohlweg's observations to warrant further study,

TABLE 1. AVERAGE WEIGHTS OF THE PITUITARY GLANDS AND OVARIES OF RATS AND RABBITS INJECTED WITH LARGE DOSES OF ESTROGENIC SUBSTANCE FOR VARYING PERIODS.

Test Animal	Estrogenic Substance Administered Daily	Average weight of Both Ovaries		Average Weight of Pituitary	
		Control mg.	Treated mg.	Control mg.	Treated mg.
Infantile rat	500 R.U. once	15	21.5		
Infantile rat	500 R.U. for 7 days	22	29	4	5.5
Infantile rabbit	12,000 R.U. for 7 days	58	60	18	17
Adult rabbit	10,000 R.U. for 7 days	230	378	18	18
Infantile rat	100 R.U. for 30 days	24	15	7	7
Adult rat	100 R.U. for 30 days	56	81	12	18
Infantile rabbit	10,000 R.U. for 21 days	65	92	18	18
Adult rabbit	10,000 R.U. for 21 days	260	190	18	19

the remaining series of experiments were executed in order to observe the ovarian and hypophyseal effects of estrogenic-substance administration to animals in varied doses and for different periods of time.

Ovarian and hypophyseal effects of large, daily doses of estrogenic substances administered over short periods to rats and rabbits

Infantile rats. Thirty of 41 infantile (35-40 gm.) rats were each injected with 500 R.U. of estrogenic substance daily for 7 days; the remaining 11

See illustrations on opposite page

Fig. 1. Infantile rat ovaries: A, control animal; B, animal given a single injection of 500 R.U. of progynon-B 7 days earlier, showing increase in total size, several maturing follicles and a corpus luteum. ×42.

Fig. 2. Infantile rat ovaries: A, control animal; B, animal given 500 R.U. of progynon-B daily for 7 days, showing mature follicles and a corpus luteum; C, animal given 100 R.U. of progynon-D daily for 30 days (practically same total dose), showing absence of expected natural follicular growth and of corpora lutea. ×63.

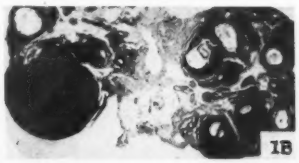
Fig. 3. Sections of anterior hypophyses of infantile rats: A, control animal; B, animal given 100 R.U. of progynon-B daily for 7 days, showing very slight increase in number of eosinophile cells. ×750.

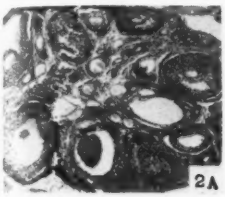
Fig. 4. Infantile rabbit ovaries: A, control animal, showing myriads of primordial follicles; B, animal given 12,000 R.U. of progynon-D daily for 7 days, showing many almost mature follicles; C, animal given 10,000 R.U. of progynon-D daily for 21 days, showing fewer follicles and dense growth of interstitial tissue. ×63.

Fig. 5. Sections of anterior hypophyses of infantile rabbits: A, control animal; B, animal given 12,000 R.U. progynon-D daily for 7 days, showing diffuse increase of eosinophile cells with variations of the cytoplasmic granules; C, animal given 10,000 R.U. of progynon-D daily for 21 days, showing even greater increase of eosinophile cells. ×750.

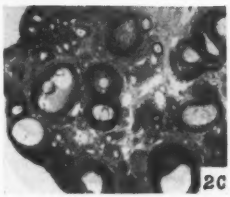
Fig. 6. Adult rabbit ovaries: A, control; B, given 10,000 R.U. of progynon-D daily for 7 days; C, given 10,000 R.U. of progynon-D daily for 21 days. Note enormous growth as result of short-term treatment and regression as result of long-term treatment. ×12.

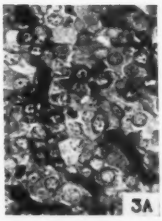
1A

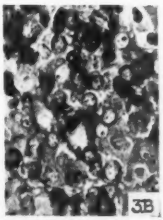

1B

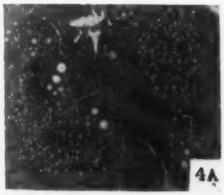

2A

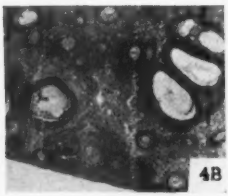
2B

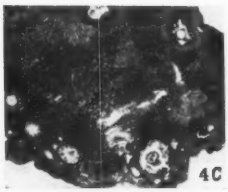

2C

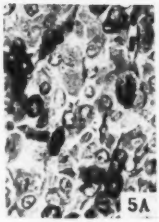

3A

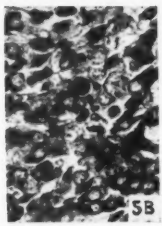

3B

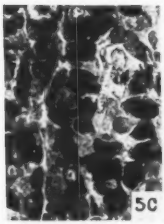

4A

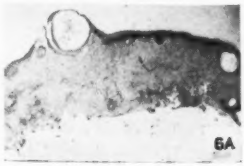

4B

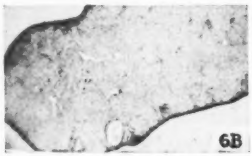

4C


5A


5B


5C

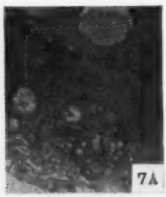

6A

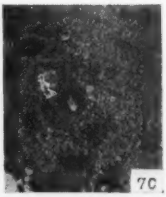

6B

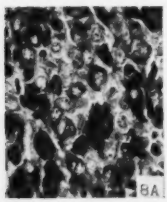
6C

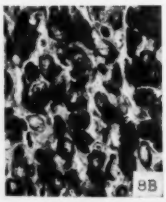
See opposite page for legend

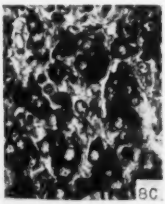
animals were untreated and served as controls. All animals were killed on the 8th day of the experiment. The ovaries of the 30 treated animals were greater in size and more globular in shape than those of the 11 controls. The average

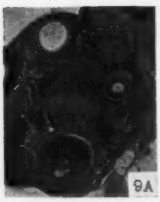


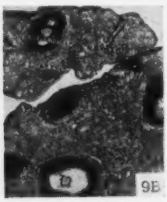


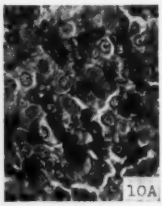


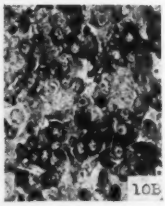


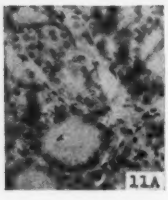












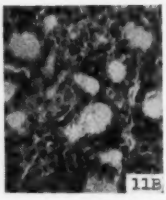


Fig. 7. Adult rabbit ovaries: A, control animal, showing several almost mature follicles; B, marked growth of interstitial tissue but no changes in follicular structure; C, showing marked follicle atresia and fibrous interstitial tissue as a result of long-term treatment. ×63.

Fig. 8. Sections of anterior hypophyses of adult rabbits: A, control; B, animal given 10,000 R.U. of progynon-D daily for 7 days, showing increased number of eosinophile cells; C, animal given 10,000 R.U. of progynon-D daily for 21 days, showing diffuse hyperplasia of eosinophile cells. ×750.

Fig. 9. Adult rat ovaries: A, control, showing corpus luteum and maturing follicles; B, animal given 100 R.U. of progynon-B daily for 30 days, showing edema of interstitial tissue, decreased number of follicles and no corpora lutea. ×63.

Fig. 10. Sections of anterior hypophyses of adult rats: A, control; B, animal given 100 R.U. of progynon-B daily for 30 days, showing no changes. ×750.

Fig. 11. Sections of thyroid glands of adult rabbits: A, control animal, showing acini containing little colloid and lined by cuboidal cells; B, animal given 10,000 R.U. of progynon-D daily for 7 days, showing no changes. C, animal given 10,000 R.U. of progynon-D daily for 21 days, showing acini filled with colloid and lined by flat cells with pycnotic nuclei. ×377.

weight of both ovaries of the control animals was 22 mg. and of the treated animals 29 mg. Several growing follicles were present in each of the control ovaries but no corpora lutea or totally mature follicles. The ovaries of the treated animals showed from 6 to 10 mature follicles and varying numbers of

developing follicles. Corpora lutea were found in one or both ovaries in 22 of the 30 treated rats (fig. 2). The pituitary glands of the control and treated groups were grossly similar and no differences in weight were observed. Histologically, the anterior pituitary lobes of the treated animals showed a very slight increase in the number of eosinophile cells but no changes in the basophile or chromophobe elements (fig. 3).

Infantile rabbits. Twelve of 18 isolated, infantile (2.5 months) rabbits were each injected with 12,000 R.U. of estrogenic substance daily for 7 days; the remaining 6 animals were untreated and served as controls. The animals were killed on the 8th day of the experiment. The average weights of the ovaries in the 2 groups showed little difference, the controls averaging 58 mg. and the treated 60 mg. in weight. The ovaries of the 6 control animals showed myriads of primordial follicles in the peripheral zones and occasional young follicles in the central areas. The ovaries of the 12 treated rabbits showed definite follicular growth, as indicated by the presence of many almost mature follicles (fig. 4). There was no variation in the average weights of the pituitary glands of the control and treated groups. Histologically, the anterior hypophyses of the treated animals showed a diffuse increase of eosinophile cells (fig. 5). Their appearance varied considerably, depending on the coarse or fine character of the eosinophilic granules of the cytoplasm. There were no changes noted in either the basophile or chromophobe cells.

Adult rabbits. Thirteen of 18 isolated, adult (4.5 months) rabbits were each injected with 10,000 R.U. of estrogenic substance daily for 7 days; the remaining 5 animals were untreated and served as controls. The animals were killed on the 8th day of the experiment. There was a marked increase in size of the ovaries of the treated group (fig. 6). The average weight of both ovaries of the control animals was 230 mg. and that of the treated group 378 mg. Microscopically, however, no striking differences were observed, aside from the presence of more fully matured follicles in the peripheral zones of the ovaries of the 13 treated animals (fig. 7). The pituitary glands of the treated and control rabbits showed no variations in average weight. Microscropically, the anterior hypophyses of the treated animals were similar to those of the previous group, inasmuch as they showed an increase in the number of eosinophile cells and no apparent changes of either the basophile or chromophobe cells (fig. 8).

Ovarian and hypophyseal effects of large, daily doses of estrogenic substance administered over long periods to rats and rabbits

Infantile rats. Five of 8 infantile (35-40 gm.) rats were each injected with 100 R.U. of estrogenic substance daily for 30 days; the remaining 3 animals were untreated and served as controls. The animals were killed on the 31st day of the experiment. The average weight of both ovaries of the control animals was 24 mg. and that of the treated group 15 mg. The ovaries of the control animals, as was to be expected after an interval of 30 days, had progressed to the stage of luteinization and each ovary exhibited from 1 to 3 corpora lutea. On the other hand, not one ovary of the 5 treated animals showed luteinization (fig. 2). The normal ovarian growth expected during a 30-day

period had not occurred. In fact, general appearance of the ovaries of the treated series was similar to that seen in the 7-day control, infantile rats. There was no difference in the average weights of the pituitary glands of the control and treated groups. There was a mild, diffuse increase in the number of eosinophile cells in the anterior hypophyses of the treated rats in comparison with the controls but no other changes (fig. 3).

Adult rats. Fourteen of 21 adult (130-150 gm.) rats were each injected with 100 R.U. of estrogenic substance daily for 30 days; the remaining 7 animals were untreated and served as controls. The animals were killed on the 31st day of the experiment. The average weight of both ovaries of the control series was 56 mg. and that of the treated animals 81 mg. The ovaries of the 7 control rats showed numerous developing follicles and corpora lutea. The ovaries of all the treated animals had an abnormal appearance, namely, an absence of corpora lutea, a decreased number of growing follicles and edema of the interstitial tissue (fig. 9). The latter probably accounted for the relative increase in the average ovarian weight. The pituitary glands of the 2 series differed in weight, the controls averaged 12 mg. and the treated 18 mg. Microscopically, however, the anterior hypophyses of the treated group showed little alteration in comparison with those of the control series (fig. 10). Occasional sections of the former group showed a slight increase in the degree of eosinophile staining but this was not sufficiently constant to be convincing.

Infantile rabbits. Six of 9 infantile (2.5 months) rabbits were each injected with 10,000 R.U. of estrogenic substance daily for 21 days; the remaining 3 animals were untreated and served as controls. The animals were killed on the 22nd day of the experiment. The average ovarian weight of the control series was 65 mg. and that of the treated 92 mg. In comparison with those of the control series, the ovaries of the treated group showed uniformly fewer follicles and dense growth of the interstitial tissue (fig. 4). There was no variation in the average weights of the pituitary glands in the control and treated series. In comparison with the controls, there was a marked increase in the number of eosinophile cells in the anterior hypophyses of the treated animals. In the latter, the eosinophile elements were diffusely scattered throughout the anterior hypophyses to the same degree and with the same characteristics as seen in the hypophyses of the infantile rabbits treated for seven days (fig. 5). The basophile and chromophobe cells were apparently unaffected.

Adult rabbits. Eleven of 15 isolated, adult (4.5 months) rabbits were each injected with 10,000 R.U. of estrogenic substance daily for 21 days; the remaining 4 were untreated and served as controls. The animals were killed on the 22nd day of the experiment. The average weight of both ovaries of the control rabbits was 260 mg. and that of the treated 190 mg. (fig. 6). The ovaries of the control animals showed growing and mature follicles in the cortical areas. The ovaries of all the treated animals were striking because of dense overgrowth of the interstitial tissue and marked follicle atresia (fig. 7). Several of the ovaries of the treated group showed fibrous tissue in the medullary portions. The pituitary glands of the control and treated series showed no significant difference in their average weight, averaging 18 and 19 mg.

respectively. Histologically, however, the anterior hypophyses of all the treated animals showed diffuse hyperplasia of the eosinophile cells, in comparison with those of the control group (fig. 8). The degree of eosinophilic alteration was very marked, giving rise to a relative decrease in the number of chromophobe cells. The cytoplasm of the eosinophilic cells varied greatly in appearance. Most of the cells were packed with eosinophilic granules, some containing scattered granules and others only peripheral granules. The latter type of eosinophilic cells were often vacuolated. The basophile cells were apparently unaltered.

Effect of large, daily doses of estrogenic substance on the adrenals and thyroid glands of rabbits.

The adrenal glands were studied in most of the infantile and adult rabbits. Mild changes noted in the adrenals of the treated animals, in comparison with those of the control series, seemed to be present irrespective of the duration of estrogenic-substance administration. In most of the adrenals of the treated series there was an increase in size of the outer cortical cells and medullary invasion by groups of mid-zonal, cortical cells. These findings were, however, inconstant and also present in a few of the control adrenals.

The thyroid glands of 13 adult rabbits injected with 10,000 R.U. of estrogenic substance daily for 7 days showed no appreciable changes as compared with controls. Those of 11 adult rabbits injected with 10,000 R.U. of estrogenic substance daily for a period of 21 days showed, on the other hand, a marked accumulation of deeply-stained colloid and flattened cells with pycnotic nuclei. These changes indicate inactivity of the gland apparently due to inhibition of the thyrotropic function of the anterior pituitary lobe through the prolonged treatment with estrogenic substance. These findings are significant and in consonance with the regressive changes found in the ovaries of these animals (fig. 11).

DISCUSSION

We may conclude from the foregoing observations that, in contradistinction to the stimulative effect of large doses given over a short period, prolonged treatment with estrogenic substance produce definite degenerative changes in the ovaries and in the thyroid gland. In this respect our findings differ from those of Hohlweg (11) who claims to have obtained definite evidence of ovarian stimulation in adult rats treated over a period of a month with 100 R.U. of progynon-B daily.

We may tentatively assume that the ovarian changes, both stimulative and regressive, herein recorded represent purely functional alterations of the anterior hypophysis, since the accompanying morphologic changes in the pituitaries of the treated animals, irrespective of length of treatment, are the same, namely an increase in the number of eosinophiles. Neither Hohlweg nor we have thus far attempted to determine the degree of gonadotropic activity of the treated pituitaries by means of implanting them into immature mice. Further illustration of the functional depression of the anterior hypophysis of animals treated for a long period with large doses of estrogenic

substance is the histologic changes of the thyroids of the treated animals. Inasmuch as the morphology of the thyroid gland accurately reflects its functional state and inasmuch as the latter is controlled by the thyrotropic hormone of the anterior pituitary lobe, comparison of the glands of the chronically treated animals with those of the acutely treated animals leaves little doubt as to the induced state of pituitary inhibition (fig. 11). The inference may be drawn that long-continued injections of massive doses of estrogenic substance, in contrast to those given during a short period of time, not only depress the gonadotropic function of the anterior hypophysis but the thyrotropic function as well. While these limited observations do not support the contention of Hohlweg and Junkmann (13) that estrogenic substance has no effect on the thyrotropic function of the anterior hypophysis, they are in substantial agreement with the more recent work of Kippen and Loeb (14) who observed stimulation of the thyroid gland following gonadectomy in the guinea pig.

These experimental data may be profitably correlated with certain clinical observations. Thus, it is well known that large doses of estrogenic substance administered for long periods to human beings depress at least 3 of the several functions of the anterior pituitary lobe, namely the gonadotropic function (15, 16, 17), the thyrotropic function (18) and the diabetogenic function (19). That large doses, such as 300,000 R.U., given during only 1 week of the month to amenorrheic women do not depress the sex function of the anterior hypophysis but, on the contrary, apparently produce stimulative phenomena was demonstrated in 3 of 8 amenorrheic women thus treated by us (20). Two of them have been menstruating regularly during a period of 7 months and the third conceived soon after the second course of treatment and bore a healthy infant. Inasmuch as the advent of pregnancy is predicated upon the existence of a functioning corpus luteum, the inception of pregnancy in the third patient, 1 or 2 weeks after she received the second course of massive doses of estrogenic substance, is seemingly confirmatory of the experimental observations on the luteinizing action of acutely administered estrogenic substance in the infantile rat.

SUMMARY

The duration of treatment is an important factor in the pituitary-ovarian response to large doses of estrogenic substance in rats and rabbits. Single or multiple injections of massive doses of estrogenic substance during 1 week caused definite ovarian stimulation in infantile animals—corpora lutea in rodents and mature follicles in rabbits. Equally large or smaller doses of estrogenic substance given during a period of from 21 to 30 days caused ovarian degeneration in infantile animals—decrease of growing follicles and fibrosis of interstitial tissue. Corresponding experiments in adult rats and rabbits yielded similar ovarian effects.

The significance of the time element is further illustrated by the microscopic appearance of the thyroid glands of the treated rabbits. Short treatment (1 week) with massive doses of estrogenic substance produced no appreciable change in the structure of the thyroid gland, but prolonged treatment caused

the accumulation of deeply-stained colloid material and flattening of the acinar epithelium.

The histologic changes seen in the hypophyses of the treated animals, namely an increased number of eosinophile cells without changes of the basophile or chromophobe elements, cannot at present be correlated with the ovarian and thyroid changes. It is reasonable to assume that fluctuations of activity in the anterior hypophysis are responsible for the varied ovarian and thyroid responses.

We are indebted to Drs. Gregory Stragnell and Erwin Schwenk of the Schering Corporation for the generous supply of progynon-B and progynon-D employed in this experimental work.

REFERENCES

1. Smith, P. E.: Am. J. Physiol. **81:** 20. 1927.
2. Zondek, B., and S. Aschheim: Klin. Wchnschr. **6:** 248. 1927.
3. Meyer, R. K., S. L. Leonard, F. L. Hisaw and S. J. Martin: Proc. Soc. Exper. Biol. & Med. **27:** 702. 1930.
4. Leonard, S. L., R. K. Meyer and F. L. Hisaw: Endocrinology **15:** 17. 1931.
5. Smith, P. E. and E. T. Engle: Anat. Rec. **42:** 38. 1929.
6. Wolfe, J. M.: Am. J. Anat. **48:** 391. 1931.
7. Nelson, W. O.: Proc. Soc. Exper. Biol. & Med. **32:** 452. 1934.
8. Kunde, M. M., F. E. D'Amour, R. G. Gustavson and A. J. Carlson: Proc. Soc. Exper. Biol. & Med. **28:** 122. 1930.
9. Allen, E.: Reactions of Immature Monkeys (Macacus rhesus) to Injections of Ovarian Hormone. J. Morphol. **46:** 479. 1928.
10. Moore, C. R. and D. Price: Am. J. Anat. **50:** 13. 1932.
11. Hohlweg, W.: Klin. Wchnschr. **13:** 92. 1934.
12. Hohlweg, W. and K. Junkmann: Klin. Wchnschr. **11:** 321. 1932.
13. Hohlweg, W. and K. Junkmann: Arch. f. d. ges. Physiol. **232:** 148. 1933.
14. Kippen, A. A. and L. Loeb: Endocrinology **20:** 201. 1936.
15. Mazer, C. and S. L. Israel: M. Clin. North America **19:** 205. 1935.
16. Albright, F.: Endocrinology **20:** 24. 1936.
17. Frank, R. T. and U. J. Salmon: Proc. Soc. Exper. Biol. & Med. **33:** 311. 1935.
18. Kirklin, O. L. and R. M. Wilder: Proc. Staff Meetings Mayo Clinic, **11:**121. 1936.
19. Patton, P. B. and J. T. Beardwood, Jr.: The Effects of Estrogenic Substances upon Certain Cases of Diabetes Mellitus. To be Published.
20. Mazer, C. and S. L. Israel: Studies on the Optimal Dosage of Estrogenic Substances: An Experimental and Clinical Evaluation. Read before the Section on Pharmacology and Therapeutics of the American Medical Association, May, 1936.

THE EFFECT OF INTERRUPTION OF THE SUPRAOPTICO-HYPOPHYSEAL TRACTS ON THE ANTIDIURETIC, PRESSOR AND OXYTOCIC ACTIVITY OF THE POSTERIOR LOBE OF THE HYPOPHYSIS[1]

C. FISHER AND W. R. INGRAM
Institute of Neurology, Northwestern University Medical School
CHICAGO, ILLINOIS

The theory that the secretory activity of the posterior lobe of the hypophysis is regulated in the mammal and in man through a diencephalic-hypophyseal mechanism has received wide recognition, although up to the present time little positive experimental evidence has been offered in support of this contention. In a recent series of articles evidence has been presented which indicates that the secretion of the antidiuretic principle by the posterior lobe is regulated through the supraoptic nuclei of the hypothalamus and the tracts which arise from them (1, 2, 3, 4). It has been shown that when the supraoptico-hypophyseal tracts are interrupted bilaterally in the cat and monkey by appropriate lesions in the anterior hypothalamus a diabetes insipidus develops which is always associated with marked degenerative changes in the pars nervosa and atrophy of the supraoptic nuclei. Because of the constant association of atrophy of the pars nervosa with diabetes insipidus in these forms, it was concluded that this disorder is due, in final analysis, to a diminution in or total abolition of the secretion of the antidiuretic principle by this division of the pituitary. This conclusion was further borne out by our finding and that of Richter (5) that the polyuria of diabetes insipidus is primary to the polydipsia.

If there is actually a suppression of the antidiuretic function of the posterior lobe of the hypophysis when the supraoptico-hypophyseal tracts are interrupted, it should be possible to demonstrate this by assaying the atrophic glands for their antidiuretic activity. The appearance of diabetes insipidus following such interruption is in itself proof that this suppression has taken place. However, in order to obviate the criticism that the atrophy of the posterior lobe is simply a fortuitous circumstance, playing no part in the etiology of diabetes insipidus, it was decided to assay some of these atrophic glands for their antidiuretic activity. At the same time and in order to test the effect of interruption of the supraoptico-hypophyseal tracts on other activities of the posterior lobe, pressor and oxytocic assays were made.

A brief description of the degenerative changes which occur in the pars nervosa of the cat after interruption of the supraopticohypophyseal tracts will be helpful

[1] We wish to express our thanks to Dr. Oliver Kamm of Parke-Davis and Company for his kindness in collaborating with us in this investigation. We also desire to thank Mr. L. W. Rowe and Dr. I. W. Grote of Parke-Davis and Company for conducting the pressor, oxytocic and antidiuretic assays, the results of which are reported in this paper.

at this point. The gland shows considerable shrinkage in size, resulting in a widening of the interglandular cleft. At the same time its walls thin out causing a marked increase in the size of the posterior lobe cavity. The encapsulating pars intermedia appears to be histologically normal, although it falls into wrinkles and folds to accommodate itself to the shrinkage of the pars nervosa. A peculiar colloid-like formation has been found in most instances surrounding and adherent to the pars intermedia. Further, it has been demonstrated (2) that the dense meshwork of unmyelinated nerve fibers, normally present in the pars nervosa and deriving from the supraoptico-hypophyseal tracts, is almost completely absent. The glia-like cells, known as pituicytes, appear to have degenerated. In their place is a dense accumulation of elongated cells, the exact nature of which has not been determined. There is a considerable increase in the amount of connective tissue and it seems not unlikely that the cells just mentioned represent a connective tissue element. The gross changes

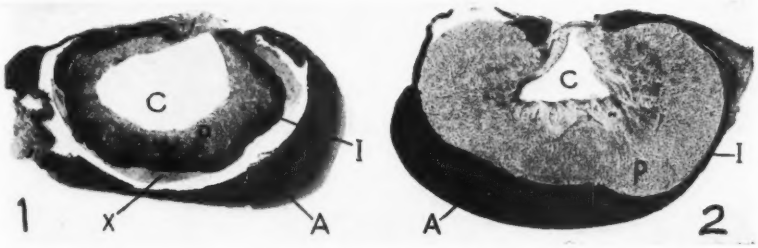


Fig. 1. Photomicrographs showing: *1*, the atrophic posterior lobe of a cat with diabetes insipidus; *2*, a normal cat posterior lobe. A, pars anteriors of hypophysis; C, cavity of posterior lobe; I, pars intermedia of hypophysis; P, pars neuralis of hypophysis; X, colloid-like ring.

described above are well illustrated in the transverse section through the atrophic posterior lobe of a polyuric cat, shown in figure 1, *1*. This figure should be compared with figure 1, *2* which represents a transverse section through a normal cat pituitary.

METHODS

Assays were made of the atrophic posterior lobes of 4 cats suffering from diabetes insipidus and of 3 normal glands. The diabetes insipidus was produced in these animals by placing lesions in the hypothalamus with the aid of the Horsley-Clarke stereotaxic instrument in the same manner as previously described (1, 2). Table 1 gives the average daily urine output, specific gravity of the urine and average daily fluid intake during the last week of survival of cats D5, D24 and D37, and during a typical week in the case of D16. As can be seen from the table, cats D5 and D37 developed marked polyurias while those of D16 and D24 were more moderate in intensity. In 3 of the animals a continuous disturbance of water metabolism was present for many months, during the entire post-operative period of survival, with the exception of the latent period preceding the onset of the permanent phase of the polyuria. The fourth animal, D37, was observed for a shorter period. The onset and development of the diabetes insipidus in these animals were in most respects similar to those reported for other animals elsewhere (1, 2).

After the period of observation the cats were killed by bleeding and the brains removed with the pituitaries attached. The entire hypophysis, including the stalk and pars tuberalis, was then cut away from the tuber cinereum and

immediately placed in acetone. The time elapsing between the death of the animal and the placing of the gland in acetone was not more than a half hour. The region of the hypothalamus was then removed from the rest of the brain, hardened in formalin, sectioned and stained with cresyl violet for cells and by Weil's method for myelin sheaths.

Extracts were prepared from each individual hypophysis in the following manner. The glands were removed from the acetone, dried, weighed and pulverized. The powder was then extracted with 5 cc. of 0.25 per cent acetic acid by heating in a water bath brought to boiling over a period of ½ hour. After slow cooling the solid residue was centrifuged out. Any active principle which might have been dissolved in the large excess of acetone used for desiccation was preserved by evaporating the acetone and dissolving the soluble portion of the residue left in the 0.25 per cent acetic acid used in extracting the pituitary. The final volume of the extract was adjusted to 5 cc. in the case of the glands from D5, D16 and normal cats 1 and 2, to 1.8 cc. in the case of D37 and normal cat 3 and to 1.9 cc. for D24.

TABLE 1. AVERAGE DAILY URINE OUTPUT, SPECIFIC GRAVITY OF THE URINE AND FLUID INTAKE DURING PERIOD OF 1 WEEK FOR CATS WITH DIABETES INSIPIDUS.

Cat No.	Length of Survival Months	Average Daily Urine Output cc.	Average Daily Fluid Intake cc.	Average Daily Specific Gravity of Urine
D5	7.5	430	381	1.011
D16	7.0	297	316	1.008
D24	7.5	293	243	1.016
D37	2.8	425	418	1.011

All the glands, the 4 atrophic and the 3 normal, were assayed for their pressor and oxytocic activity. Antidiuretic assays were made only for cats D24, D37 and normal cat 3. The methods used for the oxytocic and pressor assays will be found described in considerable detail in an article by Kamm, Aldrich, Grote, Rowe and Bugbee (6). The antidiuretic assay was performed on mice using a modification of the procedure initially described by Gibbs (7).

RESULTS

The results of the assays are summarized in table 2. The percentage potency which is indicated in column 4 depends upon the amount of solution prepared (column 3). The standard of reference for such solutions in the case of the oxytocic assays is the U.S.P. standard, which calls for 10 U. per cc. There is no official standard for pressor activity, but the pressor unit has been defined here as the amount of activity which is associated with 1 oxytocic unit in the U.S.P. standard powder. A solution which tests 10 pressor units per cc. thus is reported as 100 per cent of standard. The antidiuretic unit is defined as the amount of activity present in 0.5 mg. of the U.S. standard powdered pituitary, this unofficial unit being devised in accordance with the proposal advanced for the pressor unit (8).

Under the columns headed 'number of units' the potency of the whole gland in pressor, oxytocic and antidiuretic activity has been calculated. These

results were clear-cut. Whereas the normal glands contained 7.5, 6.0 and 5.4 pressor units respectively and 2.5, 3.5. and 2.2 oxytocic units, the atrophic glands were found to be practically inactive. Thus, the glands of D5 and D16 contained less than 0.25 U. of either pressor or oxytocic substance, that of D24 less than 0.39 pressor units and less than 0.19 oxytocic units, while that of D37 had less than 0.36 pressor units and less than 0.18 oxytocic units.

A similar marked diminution was found in the antidiuretic activity of the atrophic glands. The gland of normal cat 3 was found to contain 4.0 antidiuretic units, while those of D24 and D37 contained less than 0.23 and 0.29 U. respectively. The antidiuretic assay already referred to is that used in the Parke-Davis Research Laboratory. It is reasonably accurate when due

TABLE 2. THE CONTENT OF 3 NORMAL AND 4 ATROPHIC PITUITARIES IN PRESSOR, OXYTOCIC AND ANTIDIURETIC ACTIVITIES.

Cat No.	Dry Weight mg.	Vol. of Extract cc.	Pressor Assay		Oxytocic Assay		Antidiuretic Assay	
			Per Cent of Standard	No. of Units	Per Cent of Standard	No. of Units	Per Cent of Standard	No. of Units
Normal Glands								
1	8.29	5.0	15	7.5	5	2.5		
2	6.26	5.0	12	6.0	7	3.5		
3	8.71	1.8	30	5.4	12	2.2	15–30	4.0
Atrophic Glands								
D5	5.55	5.0	<0.5	<0.25	<0.5	<0.25		
D16	5.67	5.0	<0.5	<0.25	<0.5	<0.25		
D24	6.37	1.9	<2.0	<0.39	<1.0	<0.19	<1.2	<0.23
D37	7.26	1.8	<2.0	<0.36	<1.0	<0.18	<1.6	<0.29

precautions are observed, especially in respect to temperature control and the use of a fairly large number of animals. The mouse, unfortunately, requires a relatively large dose so that only a smaller number of animals could be run on the amount of extract available from an individual gland.

DISCUSSION

These results, together with those previously published (1, 2, 3, 4) and briefly summarized in the first paragraph of this paper, would appear to prove two things. First, they indicate that in diabetes insipidus there is a marked diminution or total abolition of the antidiuretic principle in the animal organism. It has been shown that the only lesions of the hypothalamus which produce diabetes insipidus are those which result in an atrophy of the posterior lobe. A deficiency in the secretion of the antidiuretic principle by the posterior lobe can reasonably be inferred from this atrophy alone. That the latter is not an accidental circumstance is shown further by the results reported in this paper, which indicate clearly that the degenerative changes in the pars nervosa have resulted in its physiological inactivity. The circle of evidence in favor of the deficiency theory of diabetes insipidus is finally closed by the well known

fact that extracts of the posterior lobe can control the polyuria and polydipsia of this disorder.

Secondly, these results show that, not only is the secretion of the antidiuretic principle of the posterior lobe under the control of the hypothalamico-hypophyseal system, but also the secretion of the pressor and oxytocic components. For it has been demonstrated that after appropriate damage to this system these components can no longer be extracted from the hypophysis or at best are present in extremely minute quantities.

The results of the antidiuretic assays reported here are confirmed by some preliminary observations we have made using a different type of assay. An attempt was made to check the polyuria and polydipsia of a diabetic cat with extracts prepared from single normal cat pituitaries. The method used in preparing these extracts was the same as that described above. On two different occasions, each time using the extract of a single cat pituitary, we were able to bring about a diminution in the water exchange of a cat with polyuria (400-600 cc. daily) to less than half. On the other hand, with a similar extract prepared from the atrophic gland of a cat with a 500 cc. polyuria no such marked reduction occurred.

Since the glands from the 4 polyuric cats were used to make extracts, it was, of course, impossible to check them histologically for the presence of atrophy. That such an atrophy was present, however is indicated by the following observations. First, the shrinkage of the gland is marked enough so that it can be observed grossly. Secondly, in something like 40 cats in which diabetes insipidus was produced in the same manner as in the 4 cats used in this investigation the degenerative changes which have been described were always observed in serial sections of the hypophysis. And thirdly, in the stained sections of the hypothalamus of each of these 4 animals, lesions were found which were in a position to interrupt the supraoptico-hypophyseal tracts; in each instance there was marked atrophy of the supraoptic nuclei.

Many investigators have favored the theory that diabetes insipidus is due to a disturbance of the secretion of the antidiuretic principle by the posterior lobe but little evidence has been presented in proof of this theory. A number of workers have attempted to show an absence of the posterior lobe hormones in the cisternal fluid of patients suffering from diabetes insipidus but the results from this line of attack have been conflicting. Further doubt has been thrown on the validity of this method of procedure by the inability of several recent investigators to demonstrate the presence of the pressor, antidiuretic and oxytocic components of the post-pituitary gland in the cerebrospinal fluid of normal individuals 9, 10. From the positive side, Marx (11) was able to demonstrate some decrease in the amount of antidiuretic substance in the blood of a patient suffering from diabetes insipidus.

The only other assays of single cat pituitaries that we have come across have been reported by Simon and Kardos (12). Their pressor assays are in good agreement with our own, the number of units in the glands of 10 cats averaging 8.9. They report that in the different animals which they have studied, the rat, guinea pig, rabbit, and cat, the pressor and oxytocic contents

run nearly parallel. Thus, for the cat their oxytocic assays were considerably higher than those reported here, the average number of units in the glands of 4 cats being 6.9. No antidiuretic assays were reported.

It should be noted that we have spoken of the antidiuretic and pressor components as separate principles. It is well known, however, that the antidiuretic effect is obtained with the pressor principle and recent work suggests that the chief function of the latter may be in the regulation of water metabolism. Thus, Stehle (13) was able to obtain antidiuretic effects with doses of pressor substance which were too minute to give a pressor action. He makes the suggestion that the function of the pressor principle may be more concerned with water metabolism than with the vascular system. Geiling (14) has pointed out that in man therapeutic doses of either solutions of pituitary U.S.P. or of pitressin given intramuscularly or subcutaneously do not give any significant rise of blood pressure in spite of the marked pallor, which would lead one to infer that the arterial tension is elevated. He concludes that possibly the pressor component acts as an efficient regulator of the exchange of metabolites between the blood and tissues (capillary hormone) and exercises a renal function. Kamm (15) advises us that his study of the antidiuretic activities of a large number of posterior lobe extracts, including crude extracts, partially purified products, and pitressin of the highest purity, has shown that the pressor assay is a quantitative measure of the antidiuretic activity of a given product. This result indicates fairly definitely that the pressor and antidiuretic responses are two physiological effects of a single active principle.

The results reported here lend no support to the theory that the pars tuberalis takes over the antidiuretic function of the posterior lobe when the latter is destroyed, as advocated by Frank (16) and others. As has been noted, the extracts were made of the entire hypophysis, including the pars tuberalis and stalk, but in spite of this there was a marked decrease or total abolition of the pressor-antidiuretic activity.

The term 'posterior lobe' has been used here in a broad way to include the pars nervosa and the pars intermedia. The problem arises as to the site of formation of the pressor-antidiuretic and oxytocic hormones. Until recently a definite solution to this problem was not forthcoming because in most mammals the pars intermedia surrounds and is so closely adherent to the pars nervosa that it is impossible to effect a complete separation between them. Because of the neural origin of the pars nervosa most investigators have been reluctant to ascribe a secretory function to it. However, DeLawder, Tarr and Geiling (17) and Geiling (18) have shown that in forms like the domestic fowl and in the finback and sperm whales, which are mammals, and which do not possess a pars intermedia, the pressor-antidiuretic and oxytocic components can be extracted from the pars nervosa. In the atrophic posterior lobes of polyuric cats we have always been impressed by the fact that the degenerative changes appear to be confined exclusively to the pars nervosa, the pars intermedia being histologically normal. It is true that a number of investigators have reported that some of the fibers from the supraoptico-hypophyseal tracts penetrate into the pars intermedia, but in our experience the number of these

is very small. As Geiling (18) has pointed out, the simplest explanation in harmony with the facts is that the pressor, antidiuretic and oxytocic components are formed by the intrinsic elements of the neural lobe, even though none of its structures, with the exception perhaps of the pituicytes, are regarded as secreting elements in the ordinary sense. And in this connection it is important to note that the pituicytes appear to have undergone degeneration in the non-functional, atrophic pars nervosa which results from interruption of the supra-optico-hypophyseal tracts.

In his recent summary article on the posterior lobe, Geiling (14) has remarked that in spite of the huge volume of work on the posterior lobe secretion one cannot assign with certainty any specific physiologic rôle in the animal economy to this potent autopharmacologic agent. We believe that the function of checking the flow of water from the animal organism can be assigned to the pars nervosa with impunity and a fair amount of certainty on the basis of the results reported here and in previous articles.

SUMMARY

The results of assays carried out on the atrophic post-pituitaries of 4 cats suffering from diabetes insipidus and 3 normal cats are reported. These results indicated that the atrophic glands were practically free of antidiuretic, pressor and oxytocic activity. The relationship of these findings to the deficiency theory of diabetes insipidus and to the control of the secretory activity of the posterior lobe by the hypothalamus is discussed. It is concluded that in diabetes insipidus there is a deficiency of the secretion of the antidiuretic principle and that the elaboration of this component, as well as of the pressor and oxytocic components, is under the control of the supraoptico-hypophyseal system.

REFERENCES

1. Fisher, C., W. R. Ingram, and S. W. Ranson: Arch. Neurol. & Psychiat. **34:** 124. 1935.
2. Fisher, C., W. R. Ingram, W. K. Hare, and S. W. Ranson: Anat. Rec. **63:** 29. 1935.
3. Ingram, W. R., C. Fisher, and S. W. Ransom: Arch. Int. Med. **57:** 1067. 1936.
4. Fisher, C., and W. R. Ingram: Arch. Int. Med. **58:** 117, 1936.
5. Richter, C. P.: Am. J. Physiol. **112:** 481. 1935.
6. Kamm, O., T. G. Aldrich, I. W. Grote, L. W. Rowe, and F. P. Bugbee: J. Am. Chem. Soc. **50:** 580. 1928.
7. Gibbs, O. S.: J. Pharmacol. & Exper. Therap. **40:** 129. 1930.
8. Kamm, O., T. G. Aldrich, I. W. Grote, L. W. Rowe, and F. P. Bugbee: J. Am. Chem. Soc. **50:** 579. 1928.
9. Friedman, G. S. and M. H. Friedman: Am. J. Physiol. **103:** 244, 1933.
10. Simon, A.: J. Pharmacol. & Exper. Therap. **49:** 375. 1933.
11. Marx, H.: Arch. f. exper. Path. u. Pharmakol. **176:** 24. 1934.
12. Simon, A., and Z. Kardos: Arch. f. exper. Path. u. Pharmakol. **176:** 238. 1934.
13. Stehle, R. L.: Arch. f. exper. Path. u. Pharmakol. **175:** 471. 1934.
14. Geiling, E. M. K.: J.A.M.A. **104:** 738. 1935.
15. Personal communication.
16. Frank, E.: Med. Klin. **25:** 699. 1929.
17. DeLawder, A. M., L. Tarr, and E. M. K. Geiling: J. Pharmacol. & Exper. Therap. **51:** 142. 1934.
18. Geiling, E. M. K.: Bull. Johns Hopkins Hosp. **57:** 123. 1935.

THE ENDOMETRIUM IN "ENDOMETRIAL HYPERPLASIA" AFTER THERAPY[1]

E. C. HAMBLEN

Department of Obstetrics and Gynecology, Duke University School of Medicine
DURHAM, NORTH CAROLINA

Functional meno-metrorrhagia in adolescent girls and in young women often presents a difficult clinical problem to the gynecologist who is charged with the responsibility of effective conservative therapy which avoids any possible impairment of the sexual and procreative functions of his patient. At times the radical measures of hysterectomy or large doses of x-ray or radium seem imperative to prevent exsanguination. A few fatal cases have been reported. Recently, we have encountered such a case in a colored girl, aged 15 years (1). A reliable yet innocuous method of curative therapy would fulfill a long awaited need.

As the active endocrinal preparations, which have resulted from the intensive research work of the past decade, have become available to the clinical gynecologist, application of certain of these to the treatment of such patients has been studied. As we have indicated in previous reports (2,3,4), there has been no unanimity of opinion as to the merits of such therapy. Most of these studies have been concerned with the anterior pituitary-like principle of pregnancy urine (APL/PU). We (4), as well as others, have emphasized that, despite remissions of excessive bleeding and even the occurrence of regular bleeding following such treatments, the assumption is not warranted that the underlying ovarian and endometrial pathology has been corrected. The use of estrin has been avoided rather generally in this condition and the majority of clinicians, as we have noted previously (4), have warned against its employment. The assumption that the vast majority of such bleeding was due to endometrial hyperplasia, which is apparently due to a phase of prolonged estrin action, no doubt was responsible for this attitude. Progestin has been awaited anxiously with the anticipation that it would be of therapeutic value.

This report concerns the endometrial changes observed in functional meno-metrorrhagia following therapy with large doses of progestin and of estrin and progestin.

PATHOLOGY OF FUNCTIONAL MENO-METRORRHAGIA

The term hyperplasia of the endometrium which was first used by Cullen (5) to characterize the endometrium in certain cases of functional bleeding has been used

[1] Part of the expense incurred in these studies was defrayed by a grant from the Research Council of Duke University.
Read before the Twentieth Annual Meeting of the Association for the Study of Internal Secretions, Kansas City, Mo., May 11, 1936.

rather generally to apply to all instances in which bleeding occurred from an estrin type of endometrium often being employed synonymously with aluteal or anovulatory bleeding. While our knowledge of the phenomena of menstruation is far from complete, much valuable information concerning the associated changes has accrued from the excellent work of Bartelmez (6) and of Markee (7). Our information concerning the functional histo-pathology and pathological physiology of functional uterine bleeding is rather fragmentary. It has been proven quite conclusively, however, by the studies of Schröder (8), Cullen (5), Novak (9), and Burch (10) that in this condition bleeding occurs from an estrin type of endometrium and in the absence of corpora lutea in the ovaries. Recent studies by Traut and Kuder (11) are concerned with progestational types of functional bleeding. They attach pathological significance to a process of irregular ripening which results perhaps in irregular tissue shedding associated with attendant prolonged or excessive bleeding from an endometrium exhibiting patchy progestational proliferation. Herrell and Broders (12) are of the opinion that the term endometrial hyperplasia is misapplied in many instances of functional meno-metrorrhagia where the endometrium is in the estrin phase. They believe that in many cases there is little or no evidence of endometrial hypertrophy in the strict sense of the term. Bleeding in many such cases occurs from persistent estrin or proliferative stages.

For the past 2 years we have engaged in a clinico-pathological study of 358 consecutive patients with functional irregularities of the menstrual cycle. We have correlated clinical data, reviewed and examined all available endometrial specimens secured by hysterectomy, curettage and biopsy. Ovarian tissue has been studied when available. The clinical response to various types of treatment has been considered. Where the follow-up records were not adequate, questionnaires were employed.

It was recognized at an early stage of these studies that a clinical classification of functional irregularities of the menstrual cycle which emphasized etiology and which was in harmony with the present concepts of the histology, physiology and hormonology of menstruation was desirable. We have attempted to supply such a classification. As the basis of this classification we have accepted the theory that menstrual bleeding occurs during cyclic phases of relative estrin deficiency. We have assumed that, likewise, irregular and often acyclic phases of relative estrin deficiency occur resulting in the bleeding stages of the various functional irregularities of the menstrual cycle. These bleeding phases may be characterized by normal tissue shedding, by irregular or partial tissue shedding or by no tissue loss.

Four general endometrial patterns have been observed to be associated with bleeding during the estrin phase. Variations in estrin action have been assumed to explain these patterns. The atrophic endometrium, commonly occurring after menopause, may be observed in some younger patients. It is attributed to a hypoestrin or an anestrin phase. Severe hemorrhage has occurred from such a pattern. Bleeding is observed at times from an endometrium, histologically similar to the usual early or late estrin phase. Such bleeding is interpreted as resulting from an arrest of this estrin action. A general pattern which shows considerable individual variations has been attributed to a phase of irregular estrin action. Where moderate disparity in the degree of dilatation

of the glands occurs, this type of endometrium is often referred to as endometrial hyperplasia; as a matter of fact, there is no actual evidence of proliferation or hypertrophy in these cases and we believe the concept of hyperplasia is erroneous. In other instances, the appearance of different areas of the endometrium varies; there may be observed local areas of fibrosis or of atrophy. Bleeding is attributed to an arrest of this irregular estrin action. The typical pattern of endometrial hyperplasia, including both the cystic and the relatively non-cystic types, has been attributed to a phase of prolonged and acyclic estrin action. Bleeding phases result from all these patterns when the estrin action is arrested and the estrin level becomes depressed to such extent that further proliferation and growth cannot be maintained. Bleeding in general is not characterized by tissue loss. The return of an adequate estrin level results in a non-bleeding phase which does not differ histologically from the bleeding phase.

Four general endometrial patterns have been observed also to be associated with bleeding in the progestational phase. Two of these exhibit patchy and localized distribution of progestational reaction. In one of these patterns, the predominant configuration is similar to that observed in the type attributed to a phase of irregular estrin action. This pattern is assumed to result from a progestational response following an antecedent phase of irregular estrin action. In the other pattern, the greater portion of the endometrium is characteristic of endometrial hyperplasia. This pattern is attributed to a progestational response following a phase of prolonged and acyclic estrin action. Both of these patterns represent a process of 'irregular ripening.' Bleeding results from an arrest in the estrin action. Bleeding from these two patterns may occur without appreciable tissue loss or with irregular tissue shedding or with the usual tissue loss. The latter two variations account for the remaining two patterns. The last type does not differ histologically from the menstruating endometrium.

Such concepts of the etiologic factors in the production of the various endometrial patterns suggest obvious individual differences in amenability to endocrinal therapy. The employment of estrin to convert a pattern from a bleeding to a non-bleeding phase seems logical. Furthermore, the use primarily of estrin in the treatment of the atrophic endometrium appears rational.

When our 358 patients were classified according to this system after having been divided into two general groups depending upon whether the patient was in the bleeding or the non-bleeding phase when the specimen of endometrium was obtained, the following data were secured.

The endometrium in 172 patients with functional meno-metrorrhagia (specimen obtained during the bleeding phase).

I. Bleeding in estrin phase
  A. Without appreciable tissues loss
    1. Hypoestrin or anestrin phase (atrophic or senile type) 38
    2. Regular estrin phase (interval endometrium, includes ovulational bleeding) ... 6
    3. Phase of irregular estrin action (persistent proliferative stage) 34
    4. Phase of prolonged acyclic estrin action (aluteal or interval hyperplasia) 68
II. Bleeding in progestational phase
  A. Without appreciable tissue loss
    5. Progestational phase following irregular estrin action 5
    6. Progestational phase following prolonged acyclic estrin action 4

B. 7. Progestational bleeding phase with irregular or incomplete tissue shedding.... 8
C. 8. Progestational bleeding phase with usual tissue loss (menstrual phase)..... 9

The endometrium in 186 patients with history of amenorrhea or functional meno-metrorrhagia (specimen obtained during non-bleeding phase).

Hypoestrin or anestrin phase	38
Regular estrin phase	10
Phase of irregular estrin action	60
Phase of prolonged acyclic estrin action	34
Progestational phase following irregular estrin action	35
Progestational phase following prolonged acyclic estrin action	9

It is observed from these data that 146 of our 172 patients with functional meno-metrorrhagia were bleeding from an estrin type of endometrium.

STUDIES OF QUANTITATIVE REQUIREMENTS

A review of pertinent information obtained following critical studies of the action of certain endocrine preparations upon the human ovary and endometrium seems indicated. We have reported in previous communications (2, 3, 4) that we were unable to observe either ovarian changes characterized by ovulation and corpus luteum formation or progestational changes in the endometrium following relatively large doses of APL/PU in patients under 32 years of age who demonstrated an endometrial pattern of 'swiss-cheese' hyperplasia. The administration of as much as 8200 R.U. of APL/PU in a girl aged 20 years over a period of 9 days failed to produce any such effects. In similar cases following the administration of an extract of anterior lobe of pituitary containing the gonadotropic principle we were unable likewise to observe any such changes (13). Here, however, our dosage was small due to the low concentration of the extract. The results of these studies have led us to believe that the beneficial clinical results which have been reported following such therapy are to be accounted for by changes induced in the estrin level as a result of granulosa proliferation. It seems difficult to explain any such clinical response on the basis of changes induced in certain of the bleeding factors, since we have been unable to find any significant changes in the studies of blood calcium, phosphorus, fibrinogen and cholesterol, of platelets, and of bleeding, clotting, calcium and prothrombin times before and after various types of therapy (14). In a communication (4) which dealt with studies of the endometrium obtained by the punch biopsy method following various types of therapy in patients between 14 and 34 years of age who were experiencing prolonged or excessive uterine bleeding and whose endometriums showed typical 'swiss-cheese' patterns, we reported that we were unable to find any evidence of progestational reaction following therapy distributed as follows: APL/PU, 10 patients; APE, 6 patients; moccasin venom, 7 patients; and thyroid extract, 2 patients.

There is general agreement that estrin is capable of producing definite proliferative changes in the atrophic endometrium of the castrate. Werner and Collier (15) found that a proliferative endometrium could be produced following the administration of 2800 R.U. of ketohydroxyestrin over a period of 14 days or longer in the human castrate. From such an endometrium bleeding subsequently occurred. Elden (16) has observed that the administration of 30,000 R.U. of benzoic acid ester of dihydroestrin over a period of 10 days produced a mid-interval endometrium in the castrate but that bleeding did not follow cessation of administration. However, the administration of 50,000 R.U. of the benzoic acid ester of dihydroestrin over a period of 15 days produced a late interval endometrium and subsequent bleeding.

In regard to progestin (or crystalline progesterone) the experimental data con-

flict somewhat. Kaufmann (17) observed that when 42,000 R.U. of benzoic acid ester of dihydroestrin was administered to a castrate over a period of 21 days and was followed by 35 Rb.U. (Clauberg units) of progestin over a period of 7 days, an initiation of bleeding from a progestational type of endometrium occurred. This work indicates that estrin when followed by progestin is able to substitute as regards

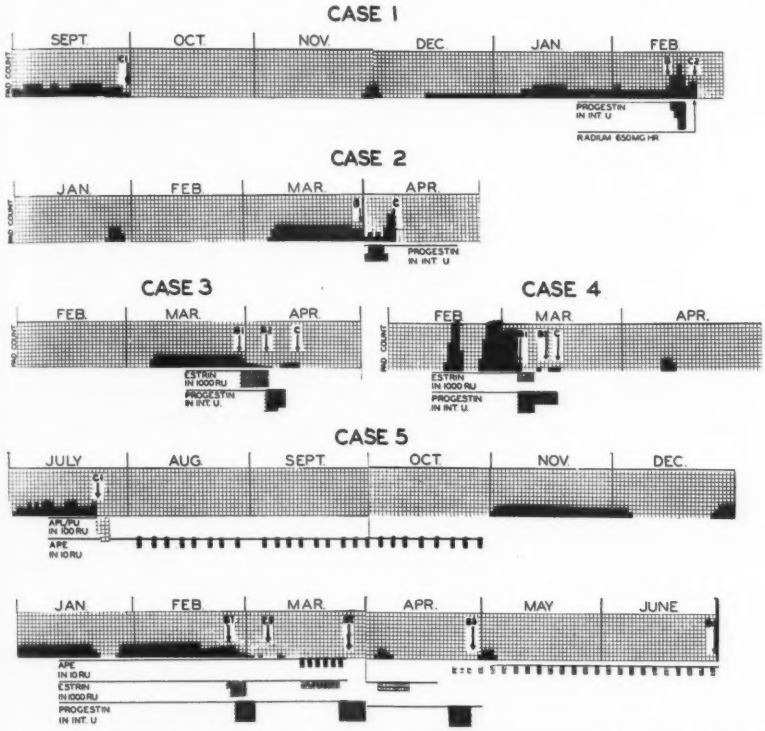


Chart I. Menstrual charts and records of therapy, biopsies and curettements in cases 1, 2, 3, 4, and 5. *Case 1,* S. G., white, age 30 years, para 0-0-0, had had prolonged, excessive uterine bleeding with varying periods of amenorrhea for 2½ years. *Case 2,* A. W., white, age 23 years, para 1-0-0, had had irregular periods of amenorrhea for 4 years. Her first prolonged and excessive episode of bleeding occurred in March. *Case 3,* T. H., colored, age 26 years, para 1-1-0, had had prolonged excessive uterine bleeding with varying periods of amenorrhea for 5 years. The prolonged bleeding which occurred in March had been preceded by 4 months of amenorrhea. *Case 4,* R. W. white, age 17 years, single, had had prolonged excessive bleeding with varying intervals of amenorrhea since menarche at the age of 15 years. At the time of admission, March 4, she was bleeding excessively and her hemoglobin was 31 per cent with a red cell count of 1,770,000. *Case 5,* H. P., white, age 15 years, single, had had prolonged excessive uterine bleeding with varying intervals of amenorrhea for 6 months prior to the period covered by the menstrual chart.

endometrial proliferation for the secretion of a normal ovary. Similar results were reported by Clauberg (18). Elden (16), however, was unable to confirm the work of Kaufmann and Clauberg. He found that progestational changes could not be produced in 5 human castrates after administration of 50,000 R.U. of benzoic acid ester of dihydroestrin over periods of 15 days followed by 12 to 60 Rb.U. (Allen and Corner units) of progestin over periods of 1 to 6 days. While bleeding resulted in all instances within an average interval of 9 days after the last estrin injection, such bleeding occurred from an estrin type of endometrium.

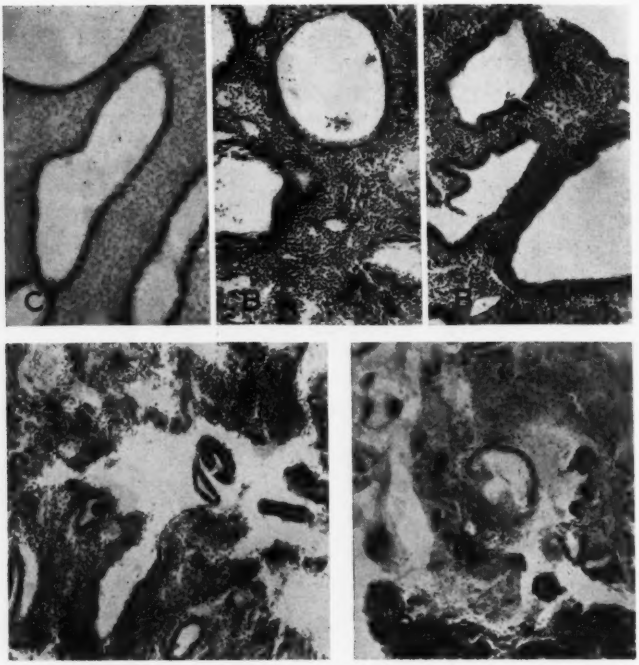


Fig. 1. Photomicrographs of endometrial specimens, case 1.

DATA AND ANALYSIS OF FINDINGS

This report is concerned with the study of the endometrium in 8 patients whose ages varied from 15 years to 30 years. The endometrium prior to the

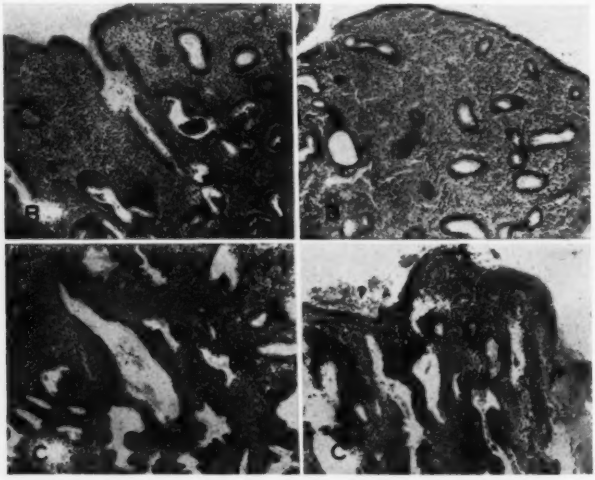


Fig. 2. Photomicrographs of endometrial specimens, Case 2.

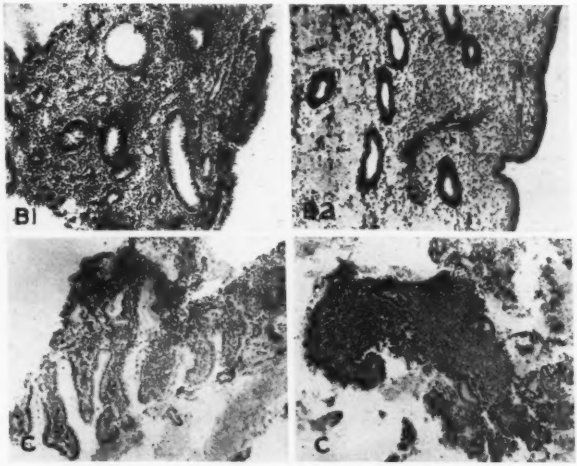


Fig. 3. Photomicrographs of endometrial specimens, case 3.

institution of therapy showed either a phase of prolonged acyclic estrin action or a phase of irregular estrin action. The specimens of endometrium were obtained by the employment of the punch biopsy forceps devised by Burch. Such a method allows small portions of endometrium to be removed for study with the minimum amount of traumatism to the remaining endometrium and offers, in our opinion, the best method of critical evaluation of endometrial changes during therapy. The tissue obtained was fixed in 10 per cent formalin and stained with hematoxylin and eosin.

In 3 of these 8 cases the total amount of progestin employed was small (less than 5 Clauberg units) due to the scarcity of the principle available and due to the lack of concentration of the preparation, and an analysis of our

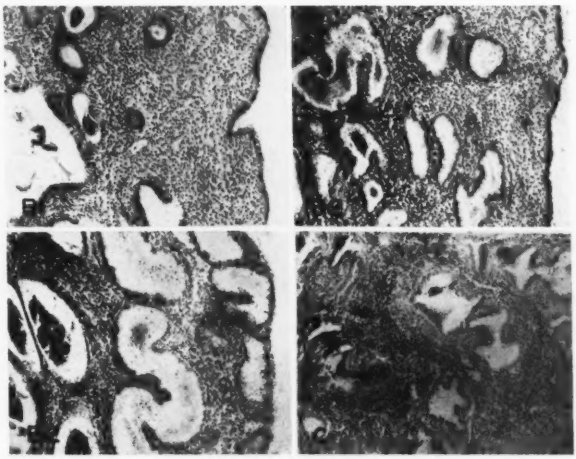


Fig. 4. Photomicrographs of endometrial specimens, case 4.

results in these 3 cases does not appear warranted. The data in the other 5 cases are presented graphically in Chart I.

In the menstrual records presented in this chart endometrial biopsis are

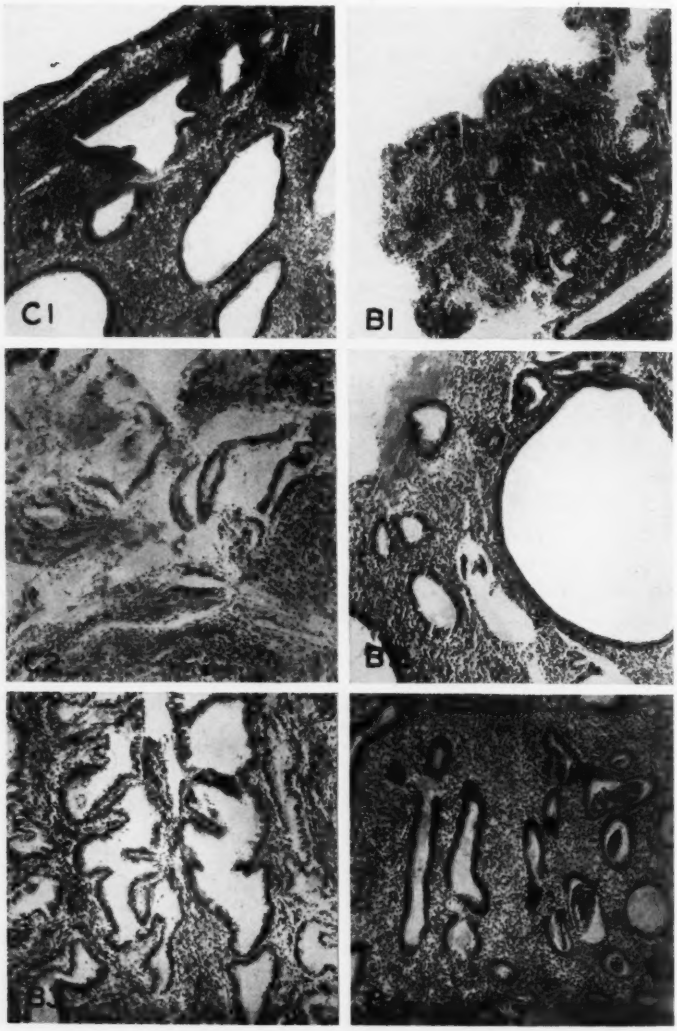


Fig. 5. Photomicrographs of endometrial specimens, case 5.

designated by *B* and the curettements by *C*. It will be observed that in all 5 of these cases the tissue following the conclusion of therapy was obtained by curettage in order that as much endometrium as possible would be available for study. An increase in the amount of bleeding during or following therapy or

a return of bleeding after therapy determined the time of this curettement. Since these curettements were done, no inferences may be drawn as to the permanency of the effects of such therapy except, perhaps, in case 5 where there was a return of irregular bleeding despite therapy and currettage.

The endometrial findings observed following the various biopsies and curettements are presented in figures 1 to 5. Progestin alone was employed in cases 1 and 2; a total dosage of 20 international units was given in each instance. The endometrium in case 1 showed an arrested phase of prolonged acycylic estrin action (*C1* and *B*) prior to the initiation of therapy and there was active bleeding without any appreciable tissue loss. Bleeding increased despite therapy and curettage was done four days after the last progestin injection. A very small amount of tissue was obtained. Microscopic examination of this tissue (*C2*) showed definite tissue loss without any evidence of progestational proliferation.

The endometrium in case 2 prior to institution of therapy showed an arrested phase of irregular estrin action (*B*) with active bleeding without appreciable tissue loss. As in case 1, there was observed a definite increase in the amount of bleeding following and during the progestin therapy. Curettage was done 2 days following the last progestin injection and a relatively small amount of tissue was obtained. Examination of this tissue (*C*) showed slight irregular tissue loss. Some of the glands manifested a suggestive early progestational change.

In case 3 there was active bleeding from an endometrium showing an arrested phase of irregular estrin action (*B1*). No appreciable tissue loss was observed. Benzoic acid ester of dihydroestrin was administered in doses of 4000 R.U. daily for 7 days. Bleeding promptly decreased in amount and ceased on the 7th day. The endometrium following this therapy showed a late estrin phase with a disappearance of the very dense stroma (*B2*) observed at the first biopsy. Progestin administration was started on the last day of the estrin therapy and was continued for 5 days until a total of 23 international units was given. Bleeding recurred during the last 2 days of progestin therapy (3 days following the cessation of estrin therapy). Curettage was done 4 days following the conclusion of progestin therapy and yielded a small amount of tissue which showed obvious tissue loss and a few glands questionably of progestational type were observed (*C*).

The endometrium in case 4, prior to therapy, showed an arrested phase of prolonged acyclic estrin action with active bleeding and no appreciable tissue loss (*B1*). The therapy employed comprised the combined administration of 2,000 R.U. of benzoic acid ester of dihydroestrin and of 5 international units of progestin daily for 4 days and subsequent use of 3 international units of progestin daily for the next 6 days. The total amount of progestin employed was 38 international units. Bleeding ceased after the first day of therapy. Five days later the patient had slight bleeding for 24 hours. This was followed by slight but continued bleeding 2 days later despite continued administration of progestin. The endometrium, 4 days after cessation of estrin therapy, showed a patchy progestational response in a pattern predominantly characteristic of

prolonged, acyclic estrin action (*B2*). Some of the progestational glands contained a small amount of recent hemorrhage. The endometrium obtained at the conclusion of the therapy was small in amount, and exhibited tissue loss and progestational reaction (*C*) similar to a menstruating endometrium.

The endometrium in case 5 prior to therapy (*C1*) showed an arrested phase of prolonged acyclic estrin action associated with active bleeding and no apparent tissue loss. Despite APE therapy for 3 months, prolonged acyclic bleeding recurred, the endometrium (*B1*) exhibiting an arrested phase of irregular estrin action and the absence of appreciable tissue loss. Therapy instituted at this time comprised the administration of 18,000 R.U. of estrin and of 25 international units of progestin over a period of 8 days. Progestin injections were started on the 3rd day of the estrin therapy. Bleeding promptly decreased in amount and ceased completely on the 7th day of treatment. The endometrium 3 days later (*C2*) exhibited a phase of irregular estrin action with some beginning tissue loss and a moderate hemorrhagic infiltration of the stroma. Eight days later the patient received 2,000 R.U. of benzoic acid ester of dihydroestrin daily for 10 days, followed by the administration of 35 international units of progestin over a period of the ensuing 7 days. The endometrium on the 3rd day of the progestin injections (*B2*) showed a phase of irregular estrin action. A period of moderate bleeding of 5 days' duration began 7 days later. The endometrium (*B3*) 26 days following the onset of this bleeding and subsequent to another series of estrin and progestin (30 international units) exhibited a progestational phase following a phase of irregular estrin action. Two days later bleeding of moderate amount began and lasted 5 days. Despite APE therapy, no further bleeding occurred and the endometrium (*B4*) 2 months later exhibited a phase of irregular estrin action.

DISCUSSION

Two apparent endometrial changes have been observed following progestin therapy: one, following progestin alone, in which there occurs tissue shedding without progestational reaction and associated with increased bleeding; the other, following estrin and progestin exhibition, is characterized by a cessation of bleeding with subsequent resumption of bleeding from an endometrium showing patchy progestational proliferation and tissue shedding. One may only theorize as to the mechanism of production of the apparent effects of progestin employment alone. It is possible that its exhibition during a phase of relative estrin deficiency might depress still further the estrin level and thus induce the observed changes of increased bleeding and of shedding of an estrin-type endometrium.

The prompt cessation of bleeding following estrin and progestin therapy is attributed to the effect of the increase in estrin level. An endometrium under such estrin influence is then capable of responding to progestin. The subsequent progestational reaction is patchy in distribution since, perhaps, only the glands showing the least aberration from normal are sensitive to the progestin influence. Such views are in accord with the concept of the one-two relationship of estrin and progestin, conclusively demonstrated in many of the

laboratory animals. The employment, therefore, of estrin to check the immediate bleeding and to render the endometrium capable of response to progestin seems rational.

The amounts of progestin found necessary to produce progestational reaction in our cases have not differed materially from those required to produce similar changes in the human castrate.

Only one of our patients (case 5) permits any inference being drawn as to the permanent benefit of the endometrial changes observed following estrin and progestin therapy. Here there was a return of menstrual irregularity with a phase of irregular estrin action after the discontinuation of this treatment. Remissions from prolonged and excessive bleeding, similiar to those after curettage might be expected in these cases following the use of estrin and progestin.

SUMMARY

A clinical classification of endometrial patterns is described in which the supposed responsible functional variations in the action of the two ovarian hormones is taken as the primary basis of classification. The employment of endometrial specimens as indicators of ovarian function is stressed as a guide to rational therapy.

Studies of 5 young patients between the ages of 15 and 30 years, with excessive and prolonged anovulatory bleeding, who were treated with progestin and with estrin and progestin, are detailed. The clinical and endometrial responses are described.

It was observed that, following therapy with progestin alone, an increase in the bleeding resulted, the endometrium showing tissue shedding without the induction of progestational changes.

When estrin was given prior to progestin, there was a prompt decrease in the amount of bleeding and early cessation of this bleeding. This was an estrin effect. Following subsequent progestin exhibition a patchy progestational reaction was observed. Bleeding recurred shortly after the cessation of the estrin injections and was characterized by tissue shedding. The amount of progestin found necessary for such changes was approximately the same as that necessary in castrates.

Only one case allows inference as to the permanency of the clinical and endometrial response following estrin and progestin therapy. After discontinuation of such treatment, there was a return of menstrual irregularity and the endometrium showed a phase of irregular estrin action.

REFERENCES

1. Hamblen, E. C., and D. H. Sprunt: To be reported.
2. Hamblen, E. C.: Endocrinology **19:** 169. 1935.
3. ————, and R. A. Ross: Am. J. Obst. & Gynec. **31:** 14. 1936.
4. ————, and W. L. Thomas, Jr.: South. M. J. **29:** 269. 1936.
5. Cullen, T. S.: Canad. M. A. J. **3:** 658 1913.
6. Bartelmez, G. W.: Am. J. Obst. & Gynec. **21:** 623, 1931. Publication 443, Carnegie Institute, p. 183, 1933.
7. Markee, J. E.: Menstruation in intra-ocular endometrial transplants in Macaca mulatta, read before Am. Assn. of Anatomists, Durham, N.C., April 9-11, 1936.
8. Schröder, R.: Arch. f. Gynäk. **27:** 104. 1915.
9. Novak, E.: Am. J. Obst. **75:** 996, 1917. J.A.M.A. **75:** 292. 1920.

10. Burch, J. C., W. L. Williams and J. M. Wolfe. Surg., Gynec. and Obst. **53:** 338. 1931.
11. Traut, H. F., and A. Kuder: Surg., Gynec. and Obst. **61:** 145. 1935.
12. Herrell, W. E., and A. C. Broders: Surg., Gynec. and Obst. **61:** 751. 1935.
13. Hamblen, E. C.: Endocrinology **20:** 321. 1936.
14. Hamblen, E. C., and Anne Yates: Unpublished data.
15. Werner, A. A., and W. D. Collier: J.A.M.A. **101:** 466. 1933.
16. Elden, C. A.: Endocrinology **20:** 47. 1936.
17. Kaufman, C.: Klin. Wchnschr. **12:** 217. 1933.
18. Clauberg, C.: Zentralbl. f. Gynäk. **56:** 2460. 1932.

TREATMENT OF SEXUAL UNDERDEVELOPMENT IN THE HUMAN MALE WITH THE ANTERIOR-PITUITARY-LIKE HORMONE (A.P.L.) OF PREGNANCY URINE[1]

DANIEL L. SEXTON

From the Endocrine Clinic, Firmin Desloge Hospital, St. Louis University School of Medicine

ST. LOUIS, MISSOURI

The effects of non-descent of the testis have been clearly presented by Moore (1) whose work has established the fact that testes in most mammals can not develop properly unless they lie free in the scrotum. He has shown experimentally that the germinal epithelium of the testis undergoes degeneration when placed in the abdomen and that recovery takes place when the testis is returned to the scrotum. In man the case seems to be similar to that of animals. Wangensteen (2) working on dogs and man concluded that undescended testes remained normal until puberty and showed degenerative changes only after this period. Cooper (3) differed, being of the opinion that testis outside the scrotum after the age of 2½ to 3 years suffer a reduction in the number and size of the tubules with an increase in the intervening stroma. He found that the sooner the testis was placed in its normal position, the better the chance for normal function.

While there is no conclusive clinical proof that delayed descent or non-descent of the testis in man causes deleterious effects, it is a matter of record that very few boys at the adolescent age with cryptorchism have normal physical proportions. Observations on bilateral non-descent are most striking although variations from the normal in the unilateral group are sufficiently convincing.

In the treatment of undescended testes there are 4 courses to pursue.

1. *Observation.* This has been advocated by Drake (4) who contends that the great majority descend spontaneously by the age of 14 years and eventually become normal in size and lie in their normal position in the scrotal sac. While spontaneous descent is acknowledged to occur, it is not without risk and is only applicable through the pubescent period.

2. *Treatment by suction.* Ballinger (5) and associates have reported the successful use of this treatment in 23 of 26 cases. By a special apparatus they apply suction to the penis and testis and attribute their results to the loosening and lengthening of the spermatic cord.

3. *Surgical.* This form of treatment has been most used. It has its objections in that results are not always satisfactory. Surgery is always preferable when there is an accompanying hernia, which was found in 87 out of 100 cases of cryptorchism reported by Counseller (6). Surgery is always necessary when hormone treatment fails.

4. *Medical.* The work of Zondek and Aschheim (7) and of Smith and Engle

[1] Read before the Twentieth Annual Meeting of the Association for the Study of Internal Secretions, Kansas City, Mo., May 12, 1936.

(8) in establishing the pituitaro-gonad relationship and subsequent work by Engle (9), Lower and Johnson (10), and Evans and associates (11), in demonstrating the stimulating effect of A.P.L. on genital development, prompted its clinical use in genital underdevelopment. In the past few years reports by Schapiro (12), Goldman and Stern (13), Cohn (14), Aberle and Jenkins (15), Rubenstein (16), Dorff (17), and one by the writer (18) indicate the beneficial effect of this hormone in the treatment of cases of cryptorchism and genital underdevelopment. More recently Werner (19) and coworkers have reported the successful use of the gonadotropic extract clinically. It appears from this and other observations that the gonadotropic extract and A.P.L. act about the same although their effect on rat testes has been shown by Engle (9) to be different.

SERIES REPORT

This series comprises a group of 18 boys in whom one or both testes were located outside the scrotum or were undefinable along the genital tract, who have been treated over the past 4½ years with A.P.L. It is considered that in those cases in which the testis was undefinable, rudimentary tissue was present and developed following treatment, for in those instances in which a favorable result occurred the testis seemed to appear suddenly.

Six of the 18 cases were complicated by hernia, which in 3 instances had been repaired and orchiopexy attempted.

With but few exceptions all of these boys had careful studies which included x-ray examination of the osseous system, basal metabolism determinations, blood studies including chemistry as indicated, and special examinations when required. Changes noticed were all individual, there being evident nothing clinically constant about the group. In the physical examination, however, this was different in that those boys in the adolescent period showed overgrowth of the long bones. This was interpreted as a sign of hypogonadism.

Non-hernia group: In the 12 cases not complicated by hernia the ages ranged from 5 to 18 years. In 7, undescent* was unilateral, 5 on the right and 2 on the left, and in 5 it was bilateral. Of the 17 instances of undescended testes, 4 were in the canal, 5 were in the external ring, 7 were classified as undefinable, and one was over the pubis. After treatment the testes were definable in the scrotum in 16 of the 17 instances. In the remaining one the testis was at the external ring. In 3 of the 16 instances with descent the testes were small and frequently retracted in 2 of the 3. The period of treatment ranged between 7 and 84 weeks. Six of the 12 were treated between 8 and 16 weeks. The amount of A.P.L. administered ranged from a minimum of 1,700 R.U. over a period of 8 weeks to 54,000 R.U. over a period of 32 weeks. The average treatment in 8 cases was 4,800 R.U. Four of the subjects received 10,600 R.U., 16,800 R.U., 36,600 R.U., and 54,000 R.U. respectively.

Five of the 12 boys who were observed gave clinical evidence of hypopituitarism. Two were definitely eunuchoid in proportion, 4 showed constitutional frailty and one had normal dimensions. Complete failure of descent occurred in 1 of the 2 eunuchoid types. Response was definitely better in the

* For clarity the term 'undescent' is used for all cases in which the testis was not identified in the scrotum.

obese group than in the frail group. In the boy in whom descent completely failed to occur, improvement from a condition of undefinable testicular tissue to that of a definite testicle palpable at the external ring was noted. This boy was treated over a period of 29 weeks, receiving 11,600 R.U. of A.P.L. Two years after treatment was discontinued reëxamination showed no change in the position of this testis. No doubt mechanical obstruction prevented its descent, and surgery must be resorted to.

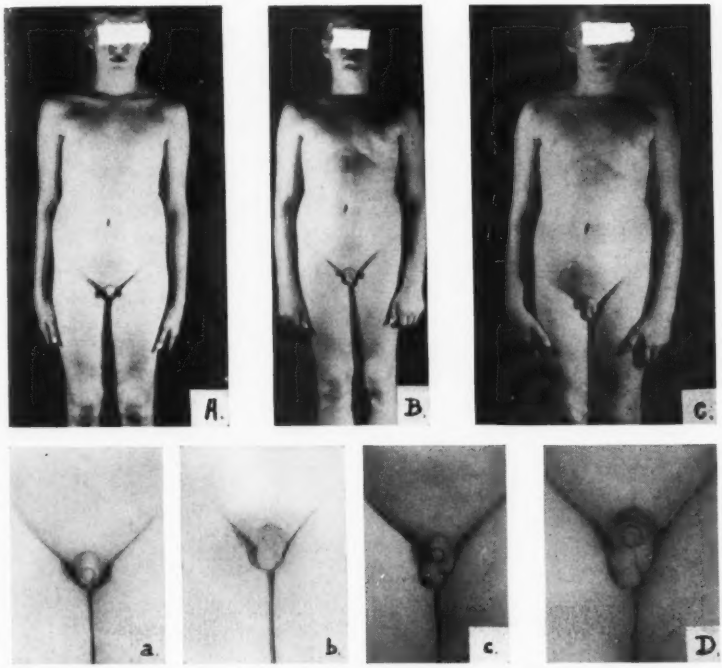


Fig. 1. Case 10, age 12½ years. *A*, Neither testicle definable. After 5,400 R.U. gonadotropic extract and 7-months' observation, right testicle was at the external ring, left testicle undefinable. *B*, After 3,600 R.U. of A.P.L. over 3-weeks' period: right testicle was in scrotum, left testicle in canal (?). *C*, After additional 27,600 R.U. of A.P.L. over 33 weeks. a, b, c, close-ups of *A*, *B*, and *C*, respectively. *D*, After additional 11,200 R.U. over 24 weeks.

Hernia group. Of the 6 cases in the hernia group, 3 had previously been operated upon. Two of the 3 were bilateral; one was unilateral, being on the left. In the unilateral case 2,800 R.U. were given over a period of 7 weeks without effect before it was learned that the left testicle had been sutured in the canal at the time of herniorrhaphy. Of the 2 bilateral cases, postoperative infection had occurred, and even massive doses over a prolonged period were ineffective in bringing about descent although secondary sex characteristics increased. In the other operative bilateral case the testicle descended from the external ring to the scrotum but remained infantile in size in spite of prolonged treatment. Three years after treatment was discontinued this testicle remains atrophic. Of the 3 cases with hernia not previously operated upon the testis

was palpable in the right canal in 2 instances before treatment. No improvement was noted in these cases after 10 and 12 weeks' treatment, respectively. In the third instance before treatment the testicle was undefinable and there was question whether or not hernia was present. After 6 weeks' therapy, in total dosage of 2,700 R.U., the hernia sac and a well-defined testicle descended into the scrotum.

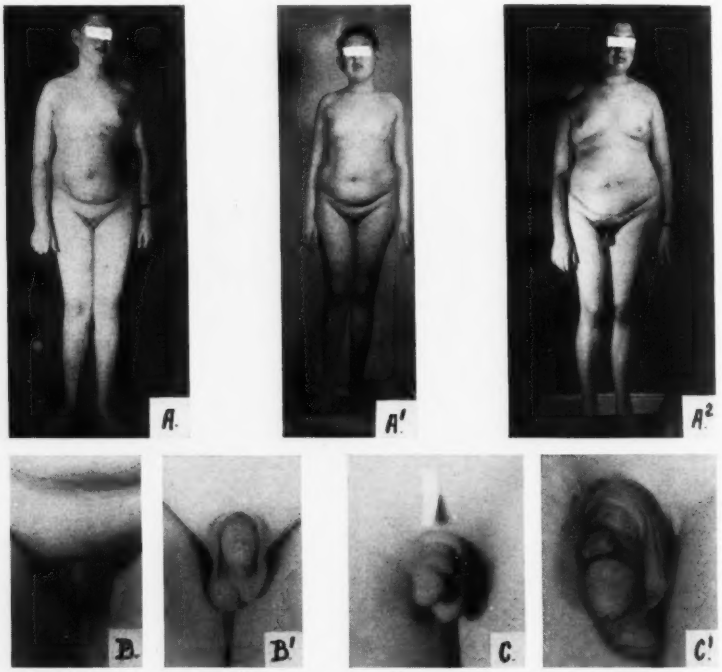


Fig. 2. Case 12, age 18 years. *A*, Left testicle undefinable; right testicle in canal. *A*¹, After 54,000 R.U. over a period of 32 weeks. *A*², Four years later, normal genital development. No treatment in interim. Case 3, age 10 years. *B*, Left testicle over pubis at point of bruise mark. *B*¹, After 3,200 R.U. over a period of 16 weeks. Case 1, age 5 years. *C*, Left testicle in inguinal canal. *C*¹, After 10 weeks' treatment with total dosage of 8,600 R.U.

In summarizing the results in the 18 cases it is only fair to eliminate the 3 operative hernia cases in which postoperative interference played a prominent role in preventing improvement. Of the remaining 15 cases (20 instances) descent occurred in 10 cases (15 instances). In 2 instances descent was incomplete. From past experience, in these two cases complete descent may be expected with continued treatment.

Report of result in 40 year old man. An additional case, not observed but treated indirectly, is worthy of report because of the advanced age. J. A., aged 40 years, of Chiz, Mexico, sought advice for bilateral undescended testes. He wrote that the external genitalia and all secondary sex characteristics were markedly underdeveloped, that the mammae were overdeveloped, and that he rarely needed to shave. At various times he had been given treatment con-

sisting of desiccated thyroid orally and injections of testicular extract, cortical substance, and other preparations suggested for his condition, all of which were without avail. Through his physician A.P.L. and desiccated thyroid were recommended. He wrote that after 40 injections of 2 cc. of A.P.L. (8,000

TABLE 1.

Case	Age Yr.	Type	Position before Tr. Lt.	Position before Tr. Rt.	Treatment Duration Weeks	Treatment Total R.U.	Position After Tr. Lt.	Position After Tr. Rt.	Final Development Normal++++ Comment
				Cases without hernia					
1	5	frail	C	S	10	8,600	S	S	++++
2	10	obese	U	C?	12	4,800	ER	S	++ Left tes. can be brought into scrotum
3	10	obese	OP	S	16	3,200	S	S	++++
4	11	normal	S	U	7	7,000	S	S	+++ Right tes. high in scrotum
5	11	frail	S	ER	16	1,800	S	S	Left tes. +++ Right tes. + (retracts)
6	11	frail	S	ER	8	1,700	S	S	+++
7	11.7	eunuchoid	S	U	29	11,600	S	ER	No change 2 yr. after treatment
8	12	frail	ER	ER	35	8,900	S	S	++
9	12	obese	U	C	33	3,300	S	S	++++
10	12.5	eunuchoid	U	U	18*	5,400*	O	O	Condition considered hopeless for surgery
					No tr. for 7 mo.				
	13.5	obese	ER	U	3	3,600	S	C?	
					3	3,600	S	ER	
					30	24,000	S	S	++ to +++
11	13.5	obese	S	ER	24	16,800	S	S	++++ after 1 yr. more of treatment
12	18	obese	U	C	16	32,000	S	S	+
					16	22,000	S	S	++ No further tr. ++++ 4 yrs later
				Cases with hernia					
13	6	frail	S	C (H)	10	1,500	S	O	Herniorrhaphy and orchiopexy
14	7	frail	S	C (H)	12	2,500	S	O	Herniorrhaphy and orchiopexy
15	7	frail	C (H)	S	7	(hern.) 2,800	O	S	Left tes. sutured in canal at oprn.
16	9	eunuchoid	S	U (H?)	6	2,700	S	S	++++ Tes. and hernia sac in scrotum
17	11	obese	S	ER	44	4,400	S	S	Lt. tes. ++++ Rt. tes. + Previous bilat. oper. After prolonged tr. and 3 yr. interval Rt. tes. + (atrophic)
18	14	eunuchoid	C	C	40	12,000	C	C	Previous bilat. oper. with P.O. infection
	14.7	obese			20	30,000	C	C	Infantile. Sparse hair growth

* Gonadotropic Extract used in first series of injections.
C—canal. S—scrotum. U—undefinable. ER—external ring. O—no change. OP—over pubis. (H)—hernia. (hern.)—herniotomy.

R.U.) the right testicle descended, and after an additional 45 injections of 300 R.U. (13,500 R.U.) the left testicle descended. The dosage of desiccated thyroid was two grains daily. The testes were reported to be the size of pigeon eggs, well situated in the scrotum. There were no appreciable constitutional changes reported. Since Pace (20) reports evidence of active tubule tissue in testes through the fourth decade, it will be of great interest to observe the final result in this case, especially regarding spermatogenesis.

TREATMENT OF SUBNORMAL GENITAL DEVELOPMENT

The effect of prolonged treatment after the testes have entered the scrotum is definitely less striking than the effect in the non-descent cases. In instances in which treatment is soon followed by descent, further development of the testis with continued treatment is relatively slow. The question has been raised as to whether or not the patient becomes refractory to prolonged treatment. The treatment of subnormal genital development with testes descended depends upon the age of the patient and degree of subdevelopment. It has become the practice of the writer to treat only those cases during the pre-adolescent age in which subdevelopment is pronounced and to observe the less advanced cases. Conservatism is lessened with the approach of pubescence.

DISCUSSION

Case 10 shows the necessity of prolonged therapy with large doses. Just how the testes in this boy arrived in the lower canal and eventually in the scrotum is not known, for there was no evidence whatever of testicular tissue detectable in the canals before treatment. It was thought by the surgical consultant who was called in the early period of treatment that both testes were intra-abdominal. It is of interest to note that cases 10 and 18 were brothers and that a maternal uncle of these boys was said to be a eunuch.

There was no instance of glycosuria or hyperglycemia following the use of A.P.L. as has been reported by Koplin (21). Likewise there were no evident deleterious changes in any of the other endocrine structures or other systems of the body following treatment.

Improvement in the psychic and general attitude following descent was indubitable. Tendencies to solitude, shyness, restlessness, and 'femininity' gave way to those characteristics expected in the normal boy. Especially was this change noted in boys at puberty who had realized their subnormal development. No satisfactory studies could be carried out for spermatogenesis before and after descent in the bilateral cases.

In those cases showing thyroid deficiency, overweight, vitamin deficiency, anemia, or any other associated or concomitant disorder appropriate treatment should be added. In the frail boys constant effort should be made to build up their general health.

SUMMARY

Eighteen boys in whom the testes were not definable in the scrotum were treated over the past 4½ years with A.P.L. Six of the 18 were complicated by hernia, 3 of which had been previously operated upon. In all 3 of these,

operative results were unsatisfactory and operative complications precluded any result from hormone treatment. Of the remaining 15 cases (20 instances) complete descent occurred in 10 cases (15 instances) and incomplete descent (intermittent retraction into canals) in 2.

The thought is advanced that in those instances in which testicular tissue is not definable in any part of the genital tract, true cryptorchism does not necessarily exist. Instead there is rudimentary testicular tissue which can not be differentiated from other soft tissues. On the average, treatment totaling 4,800 R.U. over a period of eight weeks should suffice to determine whether or not results are to be expected.

Those boys with obesity, of the pituitary types, responded more favorably than of the eunuchoid types. Treatment of subnormal genital development was less effective than the treatment of non-descent.

Clinical evidence is offered to show that delayed descent results in abnormal physical proportions with excessive long bone growth predominating.

Surgery is recommended for all cases complicated by hernia and those in which hormone treatment fails.

REFERENCES

1. Moore, C. R.: New England J. Med. **212:** 422. 1935.
2. Wangensteen, O. H.: Arch. Surg. **14:** 663. 1927.
3. Cooper, E. R. A.: J. Anat. **64:** 5. 1929.
4. Drake, C. B.: J.A.M.A. **102:** 759. 1934.
5. Ballenger, E. G., O. F. Elder and H. P. McDonald: South. Surgeon **4:** 297. 1935.
6. Counseller, V. S.: Proc. Staff Meet., Mayo Clin. **8:** 325. 1933.
7. Aschheim, S. and B. Zondek: Klin. Wchnschr. **6:** 248. 1927.
8. Smith, P. E. and E. T. Engle: Am. J. Anat. **40:** 159. 1927.
9. Engle, E. T.: Endocrinology. **16:** 405. 1932.
10. Lower, W. E. and R. L. Johnson: J. Urol. **26:** 599. 1931.
11. Evans, H. M., K. Meyer and M. E. Simpson: Memoirs of Univ. of Calif. **2.** 1933.
12. Schapiro, B.: Ztschr. f. klin. Med. **114:** 610. 1930.
13. Goldman, A. and A. Stern: New York State J. Med. **33:** 1095. 1933.
14. Cohn, S.: J.A.M.A. **103:** 103. 1934.
15. Aberle, S. B. D. and R. H. Jenkins: J.A.M.A. **103:** 314. 1934.
16. Rubenstein, H. S.: Endocrinology **20:** 192. 1936.
17. Dorff, G. B.: Am. J. Dis. Child. **50:** 1429. 1935.
18. Sexton, D. L.: Endocrinology **18:** 47. 1934.
19. Werner, A. A., D. Kelling, D. Ellersieck and G. A. Johns: J.A.M.A. **106:** 1541. 1936.
20. Pace, J. M.: Proc. Staff Meet., Mayo Clin. **10:** 726, 1935.
21. Koplin, H.: J.A.M.A. **106:** 374. 1936.

VISCERAL TEMPERATURES IN THE INTACT AND UNANAESTHETIZED ANIMAL

II. THE UTERUS OF THE RAT*

JAMES B. HAMILTON

Department of Anatomy, Yale Medical School, and Department of Physiology, Albany Medical College

ALBANY, NEW YORK

A method has been devised for determining the temperature of internal organs, which permits for the first time the use of intact and unanaesthetized animals (1). Ten abdominal organs are measured during *a*) resting conditions, *b*) metabolic changes in each organ (such as the oestrual cycle and gestation in the uterus) and *c*) physiological changes of the entire animal as in excitement or in hypothermia.

The uterus was selected as the first organ for study because of its marked physiological changes (2, 3). Uterine temperature was studied in comparison with the general body temperature under the following conditions.

A. Physiological changes particularly affecting the uterus:
   (1) The resting state, in which daily determinations were made throughout oestrual rhythms.
   (2) Pseudopregnancy, pregnancy, parturition, involution and lactation.
   (3) Retrogressive uterine changes subsequent to ovariectomy.

B. Physiological changes in the entire body:
   (4) Excitation of the sympathetic system by pinching of the tail or by fright induced by a cat.
   (5) Hyperactivity of bodily processes produced by overdoses of hormones.

PROCEDURE

A much-neglected factor in the level of body heat is the influence of the environment in which the animal has lived. Even immobilization of the rat in a thermally-controlled test chamber at 76°F. for an hour previous to testing is not sufficient to entirely overcome the effects of long-endured environmental conditions. Day-to-day variations due to this factor were eliminated in the results presented in tables 1 and 2, which compare visceral and general body temperatures. These rats were kept in a constant temperature chamber throughout the entire experiment.

Even in trained animals living in a thermally-constant animal room, the greatest regularity in daily readings is obtained only after the rat has rested for an hour in the immobilization cage; these measurements are termed 'base-line temperatures' in the tables. Tables 1 and 2 illustrate the constancy of this day-to-day base-line. The maximum temperatures listed in the tables are the degrees recorded at the onset of measurement; they exemplify the elevation of body temperature which occurs when the animal is excited and handled.

* Other organs to be reported are spleen, liver, stomach, kidney, testis and intestine.

The details of the selection and training of animals, general operative and post-operative care and the mechanical apparatus in this new technique have been given elsewhere (1). In uterine measurements a thermocouple is implanted upon the lateral side of the outer wall of the right horn at a distance arbitrarily standardized at 1 cm. below the entrance of the oviduct. Duplicate experiments were performed upon animals in which the thermocouple junction was implanted within the uterus at this same location. The approach through the abdominal wall is on the dorso-lateral surface about 1.5 cm. lateral to the mid-line of the body, the incision extending for 2 cm. rostral to the cephalic end of the innominate bone. The uterus is drawn to the incision with a minimal amount of trauma and visceral exposure by means of an adjoining fatty mesentery. After attachment the wires are passed beneath the skin for 4 cm. before penetration to the surface high on the dorsum.

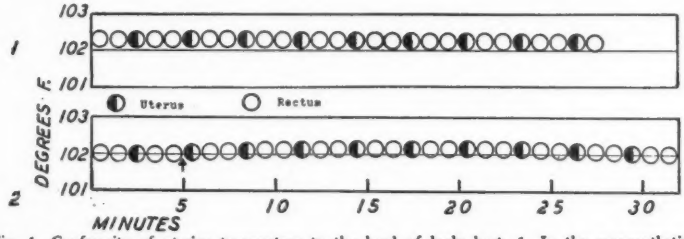


Fig. 1. Conformity of uterine temperature to the level of body heat. 1. In the unanaesthetized rat. 2. During rapid changes due to activity of sympathetic system. Arrow indicates placement of a cat close to the rat.

Technically, the long gestation period provided many difficulties in the collection of data. Daily tests resulted in the eventual breaking of the fine thermocouple wires at their connection with the machine leads, due to flattening of the wire at the set-screw contact. To overcome this, reserve spirals of wire were embedded near the thermocouple exit through the skin, and repair made by uncoiling an accessory loop. Ample protection against wire-breakage was provided by two spirals. Change in the length of wire does not invalidate readings obtained by a 'null' circuit such as that employed by the Micromax.

RESULTS AND DISCUSSION

(1) *The resting state.* Measurements were taken of 18 rats over periods ranging from 1 to 4 oestrual cycles, totalling 129 days. Table 2 shows the complete conformity of uterine temperature to the body level at all stages of the oestrual cycle despite variances in the daily level of body heat. No correlation is seen between any phase of the oestrual cycle and general body temperature, measurements of females proving no more variable than those of males. Since these rats were immobilized for an hour prior to the test, metabolic effects of oestrus as claimed by Wang and Slonaker (4) might have been eliminated, although recent claims tend to dissociate metabolism from any necessarily direct relationship to the level of body temperatures (5). Figure 1 illustrates the uniformity of temperature in successive measurements of uterine and rectal temperatures at approximately 1 minute intervals over a 28-minute period.

(2) *Pseudopregnancy, pregnancy, parturition, involution and lactation.* Pseudopregnancy induced by mechanical stimulation of the cervix at oestrus

lasted from 9 to 17 days as determined by vaginal smears. This interruption of the oestrual rhythm, like the rhythm itself, failed to disturb the conformity of uterine temperature to the body level.

Pregnancy offers a maximum of possible changes in the uterine temperature because of the enormously larger blood supply to the uterus (6), the rapid growth in size of both the organ and the enclosed embryo, and other changes incident to pregnancy. There occurred variations in the degree of uterine heat particularly in the latter half of gestation which differed 0.4 to 1.0°F. from the rectal temperature. This divergence disappeared after par-

TABLES 1–5. ANIMALS TRAINED TO REST IMMOBILIZED IN A CONSTANT TEMPERATURE CHAMBER REACH MORE UNIFORM DAY-TO-DAY LEVELS OF BODY HEAT AFTER RESTING FOR 1 HOUR; THIS IS TERMED BASE-LINE TEMPERATURE.

TABLES 2–5. DAILY MEASUREMENTS ILLUSTRATING THE CONFORMITY OF UTERINE TEMPERATURE TO THE BODY LEVEL OF HEAT AND PERSISTANCE OF THIS UNIFORMITY THROUGHOUT CHANGES IN UTERINE AND BODY METABOLISM.

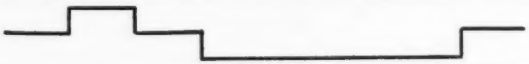
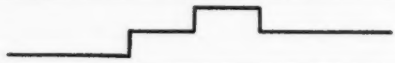
Days	1	2	3	4	5	6	7	8
Rectal Temperature								
Base-line	100.8	101.1	101.0	101.0	101.3	100.8	101.0	101.0
Maximum	101.0	101.8	101.3	101.4	102.0	101.5	102.0	101.7
Minimum	98.1	100.3	99.0	99.5	100.5	100.0	99.5	98.5
Vaginal Smear								

TABLE 2. THE OESTRUAL CYCLE. (VAGINAL SMEARS RECORDED BY METHOD OF HILL, R. T., 1932, JOURNAL OF EXPRIMENTAL ZOOLOGY, *63:* 203–234).

Days	1	2	3	4	5	6	7	8
Rectal Temperature								
Base-line	100.9	100.9	101.0	100.7	102.0	100.1		
Maximum	102.0	101.9	102.5	101.6	102.0	100.9		
Minimum	100.4	100.5	100.7	100.0	100.5	99.2		
Uterine Temperature								
Base-line	100.9	100.9	101.0	100.7	102.0	100.1		
Maximum	102.0	101.9	102.5	101.6	102.0	100.9		
Minimum	100.4	100.5	100.7	100.0	100.5	99.2		
Vaginal Smear								

turition, recurring with subsequent pregnancy and could be eliminated during pregnancy by:

(a) Removal of adhesions, when present, thereby freeing the uterus from the body wall which may be at a different temperature.

(b) Immobilization of the animal for 2-3 hours in a test chamber maintained at 82°F. Thermocouples implanted on the abdominal wall of the rat revealed the muscle wall to approximate the rectal temperature when the animal was placed in a warm environment. Hence, the wall would no longer cool the organ lying against it.

(c) Suture of the thermocouple to the medial side of the uterine horn. This procedure offered less opportunity for uterine adhesions to the body wall

and prevented contact of the thermocouple against the body wall during uterine enlargement.

In view of the thermal gradient existent in the abdominal wall of the rat which would tend to change the temperature of an organ resting upon it and in view of the thermal uniformity continually observed in other abdominal organs throughout marked physiological changes and in uterine pregnancies when contact with the abdominal wall was minimized, it is thought that the uterine temperature changes occasionally seen in a pregnant rat were not due

TABLE 3. PREGNANCY, PARTURITION, POSTPARTUM. AN UNUSUALLY LARGE LITTER OF 17 WAS BORN DURING THESE MEASUREMENTS.

Day of Pregnancy	1	2	3	4	5	6	7	8
Rectal Temperature Base-line	100.2	100.6	100.6	98.9	98.6	99.5	99.8	99.7
Uterine Temperature Base-line	100.2	100.6	100.6	98.9	98.6	99.5	99.8	99.7
Day of Pregnancy	9	10	11	12	13	14	15	16
Rectal Temp.	*	*	99.6	100.4		100.2	100.9	101.2
Uterine Temp.			99.6	100.4		100.2	100.9	**
Day of Pregnancy	17	18	19	21	21	21	21	21
Rectal Temp.	100.0	100.8	100.9	98.9	99.0	100.2	100.3	101.8
Uterine Temp.	100.0	100.8	**	**	99.0	100.2	100.3	101.8
Days Postpartum	1	2	3	4	5	6	7	8
Rectal Temperature Base-line	101.2	102.5	101.4		101.0	102.0	99.7	
Uterine Temperature Base-line	102.2	102.5	*		101.0	102.0	99.7	
Days Postpartum	9	10	11	12	18			
Rectal Temperature Base-line	100.8	101.0	100.7	*	101.2			
Uterine Temperature Base-line	100.8	101.0	100.7		101.2			

* Break in the thermocouple. An accessory spiral of wire was brought to the surface from beneath the skin. The rat was allowed 48 hours for recovery from effects of operation and anaesthesia.

** Divergence between uterine and body temperatures, which disappeared in a warm environment but re-appeared in cold surroundings. This was believed due to contact between the enlarged uterus and the cooler abdominal wall.

to any metabolic change during pregnancy. Tables 2 and 3 of uterine and rectal measurements taken previous to mating, during gestation, and post-partum, exemplify the continued uniformity of uterine and body levels of heat throughout gestation.

During parturition, pronounced vascular irregularities (7) and violent muscular contractions occur, yet readings between births of various members of the litters show the same thermal uniformity of uterine and body temperatures seen in the virgin animal. Tables 2 and 3 compare readings taken in parturition

with those taken before mating and during gestation, involution and lactation. A remarkably large litter of 17 was born to the rat whose figures are given in table 3. Readings were obtained at 3:00 P.M. after the delivery of 4 young, and at 8:00 P.M. after 9 young, at midnight after 13 young, and at 7:00 A.M. after 17 young. The rat subsequently bore a litter of 12 with the same type of thermal findings.

Likewise, the exceedingly rapid physiological involution after delivery fails to disturb the agreement of organ and body temperatures. Measurements during 26 days of lactation reveal only the usual thermal constancy.

Therefore, the conclusion seems warranted that normally occurring interruptions of the oestrual rhythm, like the cycle itself, produce no temperature variations sufficiently large to disturb thermal equilibration of the uterus and abdomen.

(3) *Retrogressive uterine changes subsequent to ovariectomy.* After total bilateral ovariectomy with removal of oviducts and ovarian capsule, the thermal integration of uterine and rectal temperatures is undisturbed, as illustrated in table 4 of readings 11-19 days after ovariectomy.

TABLE 4. OVARIECTOMY.

Days after Ovariectomy	11	12	13	14	15	16	17	18	19
Rectal Temperature Base-line	100.5	*	94.6	98.0	100.0	98.2	100.0	100.3	100.1
Uterine Temperature Base-line	100.5		94.6	98.0	100.0	98.2	100.0	100.3	100.1
Vaginal Smear									

(4) *Excitation of the sympathetic system by pinching of the tail or by fright induced by a cat.* The question then arises as to the possibility of disturbing this thermal uniformity by changes more rapid than the long oestrual rhythms or castration. Excitatory phenomena might produce an acute divergence in the mustering of the sympathetic responses of the body as described by Cannon (8). The struggle to escape from the cage following pinching of the tail occasionally served to elevate the whole body temperature but never disrupted the organ-body uniformity, for any change in the level of body heat is participated in by the uterus. The presence of a cat induced extremes from excitement to complete indifference, none of which disturbed the established thermal relationship (fig. 2).

(5) *Hyperactivity of bodily processes produced by overdoses of hormones.* Large doses of epinephrine in subcutaneous injections produced no divergence between uterine and rectal temperatures, although the body temperature was at times considerably augmented by struggle.

Daily injections of theelin (Parke-Davis) were given over a 2-week period. Aqueous solutions of 5 R.U. were injected subcutaneously each morning and evening, the uterine temperature measured at hour intervals from the time of injection until 24 hours later. A stable thermal relationship was found at all intervals. Table 5 of daily readings 1 hour after injection (since the time

required for absorptive removal of the aqueous solution may be short) reveals no difference between uterine and rectal temperatures. An oestrual condition was maintained by the administered hormone as shown by vaginal smears.

Thyroid extracts administered to 4 animals in the form of thyroglobulin did not result in any difference between uterine and rectal readings, but the number of test hours was too small to draw conclusions concerning the effect of thyroid extracts on body temperature.

Discussion is made elsewhere (9) of the capacity of an abdominal organ to remain in thermal equilibrium with the other abdominal organs throughout pharmacological variance of the body heat level and throughout radical changes of the body heat even in the entire absence of blood flow. There exists, then, in endocrinological and other physiological conditions an internal integration of heat. Inasmuch as all internal parts do not have the same metabolism or identical heat production, there must be an effective mode of thermal integra-

TABLE 5. STIMULATION BY INJECTIONS OF FEMALE SEX HORMONE, SUBCUTANEOUS INJECTIONS OF 5 R.U. (PARKE-DAVIS) DAILY.

Days	1	2	3	4	5	6	7	8	9
Rectal Temperature Base-line	101.6	99.3	102.4	102.0	101.0	100.5	102.3	101.7	101.2
Uterine Temperature Base-line	101.6	99.3	102.4	102.0	101.0	100.5	102.3	101.7	101.2
Vaginal Smear									

tion of organ and system. The data presented in this paper reveal that such thermal integration is indistinguishable whether the blood flow be reduced (uterus after castration) or increased (oestrus, pregnancy), hence, does not necessarily depend on convection by the blood stream. Conduction from tissue to tissue can maintain thermal homeostasis despite variance in and even absence of blood flow (9). Confirmation of this is given by the rats used in this report which were subjected to extreme hypothermia where no part of the animal's body was warmer than 55°F. Nevertheless, a common uterine-body level of heat was maintained whether the uterus were in a castrate or in a highly vascular condition.

This does not mean that it would be impossible to destroy the uniformity of uterine and body temperatures, for localized application of heat to the abdomen or other abnormal disturbances can overpower the equilibratory mechanisms of conduction and blood convection to give differential loci of warmth. The oestrual cycle, however, produces no such effect. The rat possesses a temperature equilibration between uterus and body that is equal to any exigency encountered in the resting state, in the physiological variations of the sexual cycle, or in physiological variations of the whole animal to which there is a secondary uterine response.

SUMMARY

The uterus of the rat has been investigated by means of a new technique which permits measurements of temperature in the internal organs of the intact

animal without exposure and without anaesthesia. The uterine temperature conforms rigidly to the level of body heat throughout all stages of the oestrual cycle. No fluctuations in the general level of body heat occur with the cycle.

This uniformity of the uterine and the body level of heat persists undisturbed during physiological changes in the uterus of pseudopregnancy, gestation, parturition, involution and lactation, and castration. Measurements included the gestation, parturition, and post partum period of a large litter of 17 young. Injections of theelin or the converse, ovariectomy, do not affect the thermal agreement between uterine and body temperature.

Changes in the level of general body heat are participated in by the uterus without detected deviation from the body level. The amount of blood in circulation through the uterus during changes in the body level does not seem to influence the thermal agreement of uterus and body, since the hyperaemic and castrate uterus respond alike to changes in the body level of heat.

There exists, then, not only a uniformity of uterine and body temperatures in the resting animal, but an internal integration that keeps organ and body at the same heat level throughout physiological and pharmacological disturbances affecting either organ or body, or both.

The author expresses his appreciation of the helpful suggestions made by Professor Edgar Allen and Harold Burr.

REFERENCES

1. Hamilton, J. B.: J. Lab. & Clin. Invest. In press.
2. Allen, Edgar. Sex and Internal Secretions. P. 410. Williams and Wilkins, Baltimore, 1932.
3. Markee, J.: Am. J. Obst. & Gynec. **17:** 205. 1929.
4. Wang, G.: Comp. Psychol. Mon. **2:** 1. 1923.
   Slonaker, J. R.: Am. J. Physiol. **68:** 294. 1924.
5. Deighton, R.: Physiol. Rev. **13:** 427. 1933.
6. Barcroft, J.: The Architecture of Physiological Function. Cambridge Comparative Physiology. Pp. 147 and 154. Macmillan, New York, 1934.
7. Knisely, H.: Proc. Soc. Exper. Biol. & Med. **32:** 212. 1934.
8. Cannon, W. B.: The Wisdom of the Body. P. 249. W. W. Norton and Co., New York, 1932.
9. Hamilton, J. B. In press.

EXTRACTS CONTAINING CORTIN[1]

FRANK A. HARTMAN AND W. D. POHLE
From the Department of Physiology,
The Ohio State University
COLUMBUS, OHIO

Since our first description of a method for the preparation of an extract containing cortin (1), we have been attempting constantly to improve the purity and yield of the hormone. Numerous methods for the preparation of cortin extracts have been described in recent years (2). Some of these have been repeated by us for comparison. Frequently the claims for potency are unwarranted because the assay employed has not been adequate. We shall describe at this time two methods which are the developments of our experiments; one is employed for the preparation of an aqueous extract to be used for injection and for chemical study; the other glycerol extract is simpler but can only be used orally for clinical study.

METHOD OF ASSAY

In order to determine the potency of our extracts in this investigation, we have used completely adrenalectomized cats. These animals were not tested until they had completely recovered from the operation and were in excellent condition. They were kept in a warm room (27-29°C.). The animals chosen for testing were in their prime as to age. Moreover only those animals with a regular appetite were selected. The same animal could be used repeatedly, provided he was brought back to excellent condition between tests. Animals allowed to become markedly insufficient often reached a condition from which recovery was either impossible or required too much time and hormone. When this happened it was more satisfactory to replace with a new test animal. The cats were fed 50 cc. of milk, 50 gm. of canned fish (salmon or mackerel) and 50 to 100 gm. of fresh beef heart. Cod liver oil (0.03 cc. per kg.) was fed 3 times a week. There was no NaCl supplement.

In assaying an extract attempts were made to start with a dosage considerably above the minimum. The extract was injected twice daily. The sum of the 2 injections is the daily dose. The quantity of extract injected was reduced every fourth day by 50 per cent if no signs of insufficiency appeared. The assay is considered to lie between the smallest quantity necessary to maintain good health and the quantity permitting the first signs of insufficiency to appear. The first reduction in food intake of a regular eater is taken as a sign of insufficiency. This is corroborated by change in behavior such as activity and response to surroundings which can best be detected by an experienced observer. Knowledge of the characteristics of each individual animal

[1] Aided by grants from the Carnegie Corporation of New York and The Rockefeller Foundation.

is very useful. In 1927 an exhaustive study was made (unpublished results of Brownell and Hartman) of blood urea as a test for adrenal insufficiency. Hundreds of urea determinations were made on 50 adrenalectomized cats. Increase in urea frequently failed to appear until long after other symptoms had developed, such as loss of appetite and change in behavior. Blood urea is neither as sensitive nor as reliable an indicator of adrenal insufficiency as appetite and behavior.

The cat unit employed in this paper is the minimum amount of hormone required daily (divided into 2 doses) to maintain an adult adrenalectomized cat in good health (without NaCl supplement).

We have compared the effects of vitamin and NaCl supplement to the diet. The control diet described above has been supplemented by the addition

TABLE 1. ASSAY ON DIFFERENT DIETS.

Diet	Extract	Cat Units per Kg. of Cortex						Average
		Cat AG 2.3 Kg.	Cat AO 2.4 Kg.	Cat W 2.8 Kg.	Cat AZ 3.1 Kg.	Cat AJ 3.2 Kg.	Cat B 3.6 Kg.	
Control	I	50>< 100	50><100	50><100	50><100	50><100		50>< 100
Control	II	50>< 100	50><100					50>< 100
Control	III						100>< 200	100>< 200
A	I	100>< 200	50><100		50><100			67>< 135
B	II	400>< 800	400><800				400>< 800	400>< 800
B	III	800><1600					800><1600	800><1600

of 0.07 cc. of cod liver oil and 1 gm. of vitavose per kg. body weight 3 times per week to make Diet A. The addition of 0.2 gm. of NaCl per kg. of body weight daily to Diet A made Diet B. Assays on these different diets are shown in table 1.

Taking into account the limitations of the assay the data show that addition of 0.2 gm. NaCl per kg. of body weight to the diet reduced the cortin requirement many fold. The amount of NaCl added was approximately equal to that contained in the food. This was shown by actual determination in samples of the food. Increase of vitamins over that in the control or regular diet was without effect.

PREPARATION OF AN AQUEOUS EXTRACT

The cortex of beef adrenals dissected free from fat and medulla on the killing floor, is frozen immediately with CO_2 snow and shipped to the laboratory in the frozen state.[2] Upon receipt it is ground while still frozen and then put into the extracting solvent. The accompanying flow sheet (table 2) outlines the method found best for routine procedure.

After shaking, the alcohol not removed by decantation is separated by pressure from the gland mass. The alcoholic extract is then filtered. In distilling the alcohol it is extremely important to stop the process before there is any appreciable thickening of the residue (vide infra). If, on the other hand, too great a volume is left the alcohol remaining prevents a differential extraction with ether. Ether for extraction must be peroxide free. We test for peroxide by the KI method, a day before use. All operations with ether are carried out in the absence of bright light. The residue is extracted 8 times with an equal volume of ether. The combined ether extractions are distilled immediately to a volume of 150 to 200 cc. Then 100 cc. of 95 per

[2] We are indebted to Doctor David Klein of the Wilson Laboratories for his cooperation in supplying the adrenal glands.

cent ethyl alcohol is added and distillation continued to previous volume to remove traces of ether. If in doubt, a second 100 cc. of alcohol is added and the process repeated.

To the residue (150 cc.) 95 per cent alcohol (700 cc.) and then water (250 cc.) are added to make approximately a 70 per cent solution. By adding 95 per cent

TABLE 2. PREPARATION OF AN AQUEOUS EXTRACT.

3 kg. adrenal cortex ground then shaken with 6 liters 90–95% ethyl alcohol 12 to 18 hrs. Filtered.	
Alcohol extract	Gland residue
Distilled in vacuo to not less than 350 cc.	
Residue	Distillate
Extracted with peroxide free ethyl ether	
Ether extract	Aqueous residue
Distilled in vacuo to 150–200 cc.	
Residue	Distillate
Taken up in 70% alcohol chilled to −20°C. and filtered	
Filtrate	Lipid residue
Distilled in vacuo to 150–200 cc.	
Residue	Distillate
Extracted with ether	
Ether extract	Aqueous residue
Distilled in vacuo to 75–100 cc.	
Residue	Distillate
Dissolved in 95% alcohol, passed through crystallite then distilled in vacuo to 25–40 cc.	
Residue taken up in water	Distillate

alcohol first, all material is kept in solution until the water is added. This prevents the fatty material from occluding the hormone as it might do if 70 per cent alcohol were added directly. The alcoholic solution is chilled at —20°C. for 24 hours or longer to precipitate lipids which are then removed by filtration at the same temperature. Vacuum distillation of the filtrate is carried out until the volume of the residue is 150 to 200 cc. This residue is extracted 8 times with an equal volume of ether as described above. The ether is removed from the combined extracts until the volume of the residue is 75 to 100 cc. The last traces of ether are removed as described above. Finally enough 95 per cent alcohol is added to make a volume of 125 cc. This alcoholic solution is passed through a tower containing 300-400 gm. of crystallite (crystallite is a product similar to permutit).

The crystallite has previously been washed with 4 per cent acetic acid to re-

move any alkali. The acid is removed by washing with 95 per cent alcohol until the washings are neutral as indicated by litmus paper. As soon as the alcohol extract has descended into the crystallite 95 per cent alcohol is added in order to keep the crystallite covered at all times until approximately 2000 cc. of alcohol has passed through the tower. The rate at the start is a drop every 2 seconds with a final rate of 2 drops per second. Passage through crystallite removes the epinephrin so that the final aqueous extract will contain less than 1:300,000. Alcohol is removed in vacuo until the residue has a volume of 25 to 40 cc. An equal volume of water is added and distillation continued to remove traces of alcohol. A decrease in the volume to less than 25 cc. is very dangerous. Water is then added to distribute the product so that 1 cc. represents 20 grams or any desired amount of cortex. NaCl is added if an isotonic solution is desired. The solution is first gravity filtered and then passed through a Seitz filter to sterilize it.

TABLE 3.

Solvent	Cat Units Per Kg. of Cortex
Acetone	32> 65
Benzol	22> 44
Ethyl alcohol, 95%	200>400
Ethyl alcohol, 87%	250>500
Ethyl ether	30> 60

Comparison of Different Solvents. We have compared the yields of cortin when the different solvents have been used for extracting the glands, all other steps in the process remaining the same. The results are shown in table 3. Ethyl alcohol is much the best. One extraction removes 90 per cent or more of the hormone. Therefore, an additional extraction seems unwarranted. Warming the alcohol-gland mixture to 40°C. at the start, apparently has no effect on the yield. Extracting the cortex with alcohol twice, the temperature starting at 70°C. each time, gave only about 1/3 of the quantity of hormone.

Acetone has been used frequently as a first solvent in other methods (3). We have repeatedly been unable to obtain good yields with it. Kendall et al (4) state that neutral acetone does not extract the hormone while acidified acetone does. We have followed the neutral acetone extraction of cortex with extraction by acidified acetone but succeeded in getting little or no hormone by the second extraction.

Purifying Solvents. The use of different solvents for purification has been studied. We have compared particularly benzol and ether. Benzol (commercial) was substituted for the ether extraction following the treatment with 70 per cent alcohol. The aqueous residue from the distillate of the 70 per cent alcohol was extracted 10 times with an equal volume of benzol. Only 15 to 20 minutes was required for each extraction because of the absence of the lipid material which was removed by chilling the 70 per cent alcohol solution. Vigorous shaking for 30 minutes did not increase the yield. From this point the procedure followed that in the chart. Our yield with this substitution of benzol extraction was only 1/5 that obtained by our standard method. If one extracts medulla by our standard method the product is toxic and therefore can not be adequately tested. Substitution of benzol for ether

seems to remove the toxicity but the yield of hormone judging from experiments on cortex alone is much below that by our standard method. This explains the need of benzol in the process when whole glands are used.

An extract was prepared using commercial $CHCl_3$ as a purifying solvent in place of ether. This extract gave an assay similar to those in which benzene was used. When C.P. ethyl acetate was employed as a purifying solvent the extract compared favorably with those made by our standard procedure.

It has also been found that the 70 per cent alcohol step may be eliminated by adding 250 cc. of H_2O in place of the 700 cc. of 95 per cent alcohol. The precipitate is separated by filtration and the aqueous filtrate extracted with ether in the usual manner. The procedure follows the chart from this point. Extracts made in this way compare favorably with those made by our regular method.

The loss of obtainable hormone must be known in order to determine the efficiency of the process. It was found that 10 per cent or less of the obtainable hormone remained in the cortex mass after one extraction with alcohol. A second extraction of the cortex would increase the ratio of foreign material to hormone, increase the time required for distilling off solvent and increase the amount of solvents used for purification. Because of these facts we believe it advisable to make only one alcohol extract of the ground cortex. The total amount of cortin in the residues of the other discarded fractions is apparently negligible.

Each method or variation was run 2 or more times and assayed 1 or more times with a variation of less than 25 per cent from the average.

Other Factors in Purification. As already pointed out excessive concentration of residues during distillation is to be avoided. If this precaution is observed material which may spatter, immediately runs back into the main body of the extract without drying on the sides of the flask. The temperature of the water bath surrounding the flask is never allowed to go above 45°C. The optimum temperature is 42-43° when one considers the speed of distillation on the one hand and the danger of drying of the spattered material on the flask, on the other. Before these precautions were appreciated and material was permitted to dry on the flask or the residue was reduced to very small volume, the yield of cortin was reduced to 1/5 of the possible yield. We now arrange our apparatus so that there is a steady flow of new extract into the flask, determined by the rate of distillation. This constant stream breaks the surface of the liquid and prevents bumping and super-heating. When distilling the ether, the temperature of the water bath is never allowed to rise above 40°C. Otherwise the precautions are the same as for alcohol distillation. The alcoholic extract from the ground cortex may be chilled at —20°C. and the precipitated lipids filtered off. Such a step reduces the time required for distillation and makes the following purification easier.

PREPARATION OF A GLYCEROL EXTRACT

Fresh ground cortex and glycerol (U.S.P.) are allowed to stand at a temperature of 4°C. for several days. This material is thoroughly shaken from time to time. Alcohol equal to the volume of glycerol is added and after

thorough shaking the glycerol-alcohol extract is filtered at 4°C. This extract is allowed to stand at —20°C. for a week or more. The precipitate which forms at this low temperature is separated by filtration. Filtration requires about one day. The filtrate is removed to a temperature of about 25°C. for 12 to 18 hours. An additional precipitate forms. This is removed by filtration. The filtrate is then passed slowly through a tower containing crystallite previously washed by acid and alcohol as described in the method for preparing an aqueous extract. Finally the extract remaining in the crystallite is washed out by alcohol. The proportions are: 3 kg. cortex to 3 liters of glycerol; 3 liters of 95 per cent alcohol to dilute the glycerol; 3 kg. of crystallite and 3 to 6 liters of 95 per cent alcohol to wash same.

The extract and washings are combined. The alcohol is removed by distillation in vacuo in a water bath held at 42-43°C. Distillation is continued until most of the alcohol has been removed, as indicated by slow discharge from the condenser. The residue is bottled and kept cold until used. The final glycerol extract contains the product of about 1.5 gm. of cortex per 1 cc.

Most glycerol extracts contain all of the epinephrin and all or a considerable amount of the gland tissue. This method removes 80 to 90 per cent of the epinephrin present. (When not treated with crystallite the extract contains about 1:500 epinephrin while treatment with crystallite reduces it to 1:5,000-10,000; the epinephrin content was assayed by the intestinal strip method.) All tissue and some precipitated matter as well as substances taken up by the crystallite are removed.

Glycerol extract has been found particularly useful in early Addison's disease or early adrenal insufficiency. It is not effective in later stages. It is cheaper to prepare and keeps better than the aqueous extract. The oral method of administration which glycerin requires is also easier.

SUMMARY

The addition of NaCl to the ordinary diet of adrenalectomized cats reduces the cortin requirement many fold. A cat unit is defined as the amount of hormone required daily to maintain an adult adrenalectomized cat in good health (without NaCl supplement). Among acetone, benzol, ethyl ether and ethyl alcohol, ethyl alcohol gives by far the greatest yield of cortin when used to extract the glands. Ethyl ether and ethyl acetate seem to be better solvents than commercial benzol and chloroform for purification. It is extremely important to avoid great concentration of residues in order to prevent spattering and drying of material on the distillation flask. An outline for the preparation of an aqueous extract is given. A glycerol extract from which a large proportion of epinephrin is removed is described. The latter has the advantage of being simpler to prepare and easier to administer.

REFERENCES

1. Hartman, F. A., C. G. MacArthur, and W. E. Hartman: Proc. Soc. Exper. Biol. & Med. **25**: 69. 1927.
2. Harrow, B., and C. P. Sherwin: The Chemistry of the Hormones, p. 124, Williams & Wilkins Co., Baltimore, 1934.
3. Kutz, R. L.: Proc. Soc. Exper. Biol. & Med. **29**: 91. 1931.
4. Kendall, E. C., H. L. Mason, B. F. McKenzie, and C. S. Myers: Proc. Am. Soc. Biol. Chem. **8**: 59. 1933.

THE GENESIS OF THYROID PROTEIN: CLINICAL ASSAYS OF ARTIFICIAL THYROID PROTEIN IN HUMAN MYXEDEMA[1]

W. T. SALTER AND J. LERMAN

From the Huntington Memorial Hospital of Harvard University and the Thyroid Clinic of the Massachusetts General Hospital

BOSTON, MASSACHUSETTS

A striking feature of iodine therapy in thyroid hyperplasia is the rapid increase in the amount of colloid stored within the gland. Associated with the fixation of iodine, as Marine and Williams (1) and others have shown, there occurs a rapid deposition of thyroglobulin, which is the characteristic protein of this endocrine organ. Nearly all of the organic iodine in the gland can be extracted and isolated in the form of this protein (2). At first, according to Gutman, Benedict, Baxter and Palmer (3), little thyroxin is stored; most of the newly deposited iodine probably consisting of diiodotyrosine in peptide linkage (4). Subsequently, as more iodine is deposited in the gland, the proportion of thyroxin becomes larger. Nevertheless, the newly deposited iodine appears to be quite as active calorigenically as thyroxin iodine (5, 6) when tested on myxedematous human subjects. This paper[2] attempts to adduce chemical and clinical evidence as to the mechanism by which inorganic iodine becomes incorporated into an active thyroid hormone (7, 8).

PLAN OF STUDY

The procedure consisted in administering artificial iodine-containing preparations in standard daily dosage to myxedematous individuals. From previous work (9) it was known that the response in basal metabolic rate of such patients could be used to gauge quantitatively the activity of the medication employed. The substances chosen for administration were 3: *a*) a preparation made from horse serum and iodine; *b*) an iodine-containing preparation made from the non-thyroxin fraction of human thyroglobulin; and *c*) an artificial protein made by enzymic synthesis from this latter substance, *b*). The source of each of these preparations, therefore, was free from thyroxin or nearly so. The latter 2 preparations were related to each other as shown in figure 1. A description of the 3 preparations follows.

CHEMICAL PREPARATIONS

A) Artificial protein from iodinated horse serum. An iodinated horse serum was prepared according to the directions of Wormall (10). Briefly, the

[1] This work was aided by a grant from the International Cancer Research Foundation, and the Ella Sachs Plotz Foundation.

Read before the Twentieth Annual Meeting of the Association for the Study of Internal Secretions, Kansas City, Mo., May 12, 1936.

[2] These data are complementary to chemical data which appeared in the paper by Salter and Pearson (16).

procedure consisted in treating horse serum with elementary iodine under appropriate conditions, which attach iodine to the serum protein. As a result, one obtained an iodo-protein preparation in which the iodine was organically bound as an integral part of the albuminous substance. Such preparations are ordinarily inert when administered to mammals (11), but Abelin has recently reported (12) that boiling with alkali will activate them to a certain extent. Accordingly, our iodinated horse protein was digested with pepsin, and after removal of unchanged protein by heat coagulation, the resulting iodo-peptone was concentrated in vacuo. Pepsin was again employed to produce peptic synthesis as described below. The effect was to recombine certain fragments

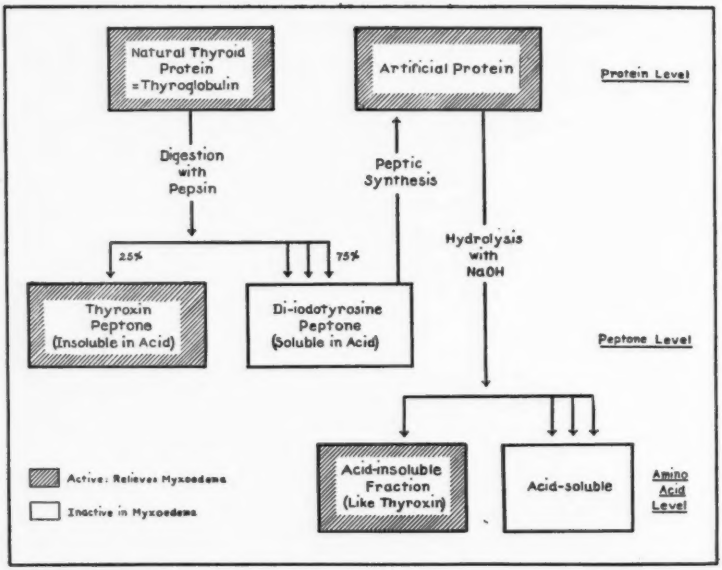


Fig. 1. Diagrammatic representation of the relationships between natural and artificial thyroid protein and their respective cleavage products.

of the proteolytic split products and there resulted an artificial iodine-containing protein. This artificially-made colloid contained 15 per cent nitrogen and 3.2 per cent iodine.

B) Diiodotyrosine peptone from human thyroglobulin. When a thick paste of purified human thyroglobulin (i.e., colloid) suspended in dilute hydrochloric acid is digested with pepsin at 37°C, Harington and Salter (13) found that digestion is practically at an end in 72 hours. At that time unchanged protein and higher proteoses can be removed by heat-coagulation and precipitation with 70 per cent acetone or with alcohol-acetone mixtures.

The solution can also be cleared of protein by filtration under pressure through a membrane suitably chosen for ultrafiltration of large molecules.[3] The thyroxin-

[3] For this purpose we have used the No. 501 high pressure apparatus obtained through Pfaltz and Bauer, Inc. (N.Y.), employing a pressure of 50 to 100 atmospheres of nitrogen gas, with cellophane, No. 300 (plain), as the membrane.

containing moiety of the peptone can be removed, as shown by Harington and Salter (13), by isoelectric precipitation.

There results, after concentration under reduced pressure, a solution of peptone containing iodine in organic combination; the iodine-bearing amino acid, according to Harington and Randall (4) and Foster (14), is probably diiodotyrosine linked to the peptone chain. The dried material contains 0.1 per cent iodine and 14 per cent nitrogen. It usually comprises over two-thirds of the total iodine in human glands in a non-goitrous district. Hitherto, this fraction has been neglected and discarded because it was presumed to be physiologically inert (4, 15).

In the present work, 2 types of excised human goitre were used as the source of hormone, i.e., non-toxic adenomatous goitre (multiple colloid adenomatous, so-called) and the hyperplastic glands from individuals with exophthalmic goitre receiving iodine before operation.

C) Artificial protein prepared by enzymic synthesis. From the diiodotyrosine preparation just described, an artificial protein can be obtained by the use of pepsin. The enzyme is allowed to act under conditions which reverse the digestive process. The result is an albuminous colloid, of high molecular size, which resembles in several features the natural thyroglobulin. It contains approximately 0.2 per cent iodine and 14 per cent nitrogen. Peculiarly enough, it also contains an iodine moiety which after hydrolysis of the protein, behaves chemically like the thyroxin moiety in natural thyroglobulin.

In short, enzymic synthesis in vitro has yielded a product which closely resembles the 'colloid' laid down by natural processes in vivo. The preparation and properties of this artificial human protein have been described in detail elsewhere (16).

CLINICAL ASSAY

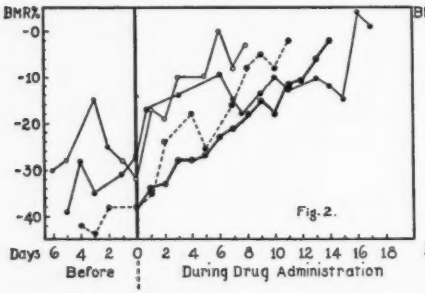
The response of individuals suffering from frank spontaneous myxedema was used to test the potency of these iodine-containing albuminous substances. A positive, marked metabolic effect would be presumptive evidence that our artificial synthesis had approximated natural transformations which occur in the economy of the body. In judging the effectiveness of the medication 3 criteria were employed: *a)* the rapidity of the calorigenic response as described by Salter, Lerman, and Means (9); *b)* the relief of clinical symptoms; in some instances, in addition, *c)* the appearance of creatinuria as described by Palmer (17) and by Shorr and Richardson (18). Of these criteria, the first was considered of greatest quantitative importance in the determination of physiologic activity.

A uniform daily dosage containing 0.5 mg. of iodine was relied upon for comparison with known effects produced by standard thyroid preparations as described previously (9). Insoluble material was dissolved in dilute alkali prior to administration by mouth.

A) Artificial protein from iodinated horse serum. Only 1 patient was used to test this substance, which yielded a negative result even though the daily dose was increased to 5 times the standard amount (i.e., up to 2.5 mg. of

iodine daily). Nevertheless, this patient subsequently made a characteristic response to U.S.P. desiccated thyroid. From the ineffectiveness of this preparation one must infer that the mere presence of iodine, organically-bound, is not sufficient to endow an artificial protein with the power to relieve myxedema. In short, the iodine must be present in a specific chemical form.

B) Diiodotyrosine peptone from human thyroglobulin. When administered in standard dosage (i.e., 0.5 mg. of iodine daily) to 5 patients, this substance failed to produce an unequivocal metabolic response. When used in larger dosage, however, 3 patients made a definite response, as judged both by clinical and calorigenic findings. At first glance, these results would seem to agree with Hutchison's (11) obtained over 30 years ago: "The soluble albumoses were active but in a very feeble degree" (in "a well marked case of myxedema"). These results are shown in figure 2.



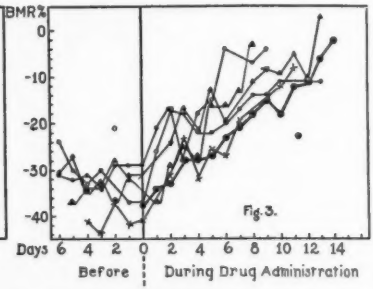


Fig. 2. The calorigenic responses of 3 patients with spontaneous myxedema to daily oral doses of diiodotyrosine peptone (containing 2.5 to 3.0 mg. of total iodine) which had been freed of thyroxin peptone and thyroglobulin by the usual chemical procedures. The heavy solid line, also present in figures 3 and 4, is the standard response to daily doses of 1.0 mg. of natural thyroxin polypeptide (0.5 mg. total iodine).

Fig. 3. The calorigenic responses of 5 patients with spontaneous myxedema to daily oral doses of artificial protein (containing 0.5 mg. of total iodine). Two patients received protein made from diiodotyrosine peptone which had undergone ultrafiltration (solid lines and solid triangles); the other 3 received protein made from diiodotyrosine peptone which had been freed of thyroxin peptone and thyroglobulin by the usual chemical procedures.

Ultra-filtered peptone. Is this activity of diiodotyrosine peptone in large doses due to an impurity or to the peptone per se? The diiodotyrosine peptone used in these 3 assays showed on chemical analysis (16) that only 4, 3 and 4 per cent, respectively, of the total iodine could be present as thyroxin. Were this present in the form of thyroglobulin (dissolved in peptone solution), however, it might account for the activity of the peptone when given in large doses.

Accordingly the diiodotyrosine solution was filtered through 'cellophane' membranes under 75 atmospheres' pressure. The filtrate when administered to 3 patients in a dose containing 2.5 to 3.5 mg. of iodine daily (i.e., 5 to 7 times the standard dosage), failed to produce a response. One of these patients subsequently received unfiltered peptone in a daily dose of 3.0 to 3.5 mg. of iodine, and made a satisfactory recovery as shown by the interrupted line in figure 2. The other 2 patients subsequently received artificial protein prepared from this ultrafiltered peptone in standard dosage (0.5 mg. of iodine daily).

These 2 patients made the expected response[4] as described in the following section, and illustrated in figure 3 (solid lines and solid triangles).

These observations, therefore, indicate that diiodotyrosine peptone when pure has a negligible effect in human myxedema.

C) Artificial protein prepared by enzymic synthesis. The artificial protein was tested in standard iodine dosage on 6 patients, all of whom gave undeniable evidence of improvement. As shown in figure 3, 5 of the results approximated the standard response obtained with thyroxin polypeptide (9) in equi-iodine dosage. The recovery rate averaged 2.6 points per day as against 2.5 points for the standard. Another positive response was obtained from the artificial protein but it was not of quantitative significance. The subject was

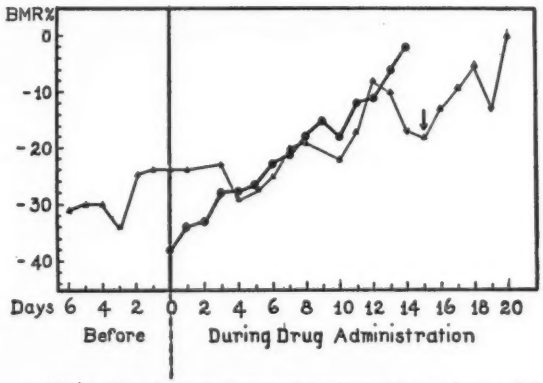


Fig. 4. The calorigenic response of 1 patient with myxedema to daily oral doses of the thyroxin-like fraction obtained from artificial protein by alkaline hydrolysis. The arrow indicates where the dosage was changed from 0.5 mg. of total iodine to 1.0 mg. of total iodine.

mildly myxedematous following thyroidectomy, and was studied in anticipation of obtaining only a qualitative result. Consequently, the metabolic data are not charted. In this case, also, the clinical symptoms definitely improved.

Of the cases charted in figure 3, three represent patients treated with artificial protein made from diiodotyrosine peptone prepared as described early in this paper. The other two (illustrated by solid lines and solid triangles) represent patients treated with artificial protein made from ultra-filtered peptone as just described.

Figure 4 shows the calorigenic response made by a markedly myxedematous patient to the thyroxin-like moiety of the artificial protein, obtained after drastic alkaline hydrolysis (see fig. 1). A complete recovery was not obtained in this patient until twice the standard dose was administered daily (indicated by arrow). Inasmuch as the drastic chemical hydrolysis would be expected to transform at least a portion of the acid-insoluble fraction into free thyroxin, this substandard effect was to be expected, because free thyroxin usually gives little effect when administered by mouth.

[4] Through the courtesy of Dr. W. W. Palmer and Dr. G. P. Leland, the ultra-filtered peptone and the artificial protein prepared therefrom were assayed in normal guinea-pigs. The results are to be reported elsewhere.

The soluble portion resulting from drastic alkaline hydrolysis (cf. fig. 1) failed in 2 patients to produce any effect in standard dosage.

DISCUSSION

It must be emphasized that the preparations here described were assayed, not in laboratory animals, but in man. Furthermore, the human individuals studied were athyreotic. Accordingly, due caution must be exercised in comparing these observations with data obtained with laboratory animals or with normal human beings. In such, different results might be obtained.

Our observations in human myxedema indicate that by enzymic action an artificial protein has been synthesized which possesses marked metabolic activity. The chief biological interest in this fact lies in the source of the material—the diiodotyrosine peptone. This fraction of the thyroglobulin molecule has hitherto been thought to be inert (19), and procedures for assay of pharmacological activity (20) have been suggested which ignore this part of the iodine in designating the potency of thyroid preparations. Thus, two-thirds of the iodine in thyroid is neglected or discarded. The marked activity of the artificial protein, however, confirms the finding of Means, Lerman and Salter (5) that in the treatment of human myxedema this acid-soluble fraction has full calorigenic activity when in natural protein combination. Forty years ago Hutchison (21) wrote: "In other words, the colloid matter is active as a whole, not merely in part."

The single amino acid diiodotyrosine contributes all of the iodine in this acid-soluble fraction according to Harington and Randall (4). This finding is striking, because there is general agreement that the pure, isolated diiodotyrosine is essentially inert in mammals (22). Even when exceedingly large doses were administered to man, Thompson and his collaborators obtained only an equivocal effect (23, 24).

The clinical observations described in the present report, moreover, indicate that when diiodotyrosine is found combined in peptide linkage with other amino acids in a long chain (to form a natural peptone), it still fails to show significant biological activity when care is taken to remove traces of thyroglobulin impurity. Nevertheless, when several such peptone chains are re-combined (by peptic synthesis) to form a molecule of colloidal dimensions, the resulting artificial protein is as active as the natural colloid, in which a considerable part of the iodine consists of thyroxin. Furthermore, this artificial protein has many of the characteristics of natural colloid, both chemical and physiological. The evidence for chemical similarity is reported elsewhere (16). The present report demonstrates that even the split products of both the artificial and the natural protein have similar biological effects.

Quantitative evidence for the artificial production of thyroid activity. The possible presence of traces of thyroxin impurity in the diiodotyrosine preparations makes it essential to control carefully this source of error. Accordingly, an arithmetical balance sheet is given to answer two pertinent questions: *a)* Could the effect of artificial protein represent merely a quantitative precipitation of thyroxin impurity from the solution of diiodotyrosine peptone? and *b)*

Could the effect of artificial protein be accounted for by its thyroxin-like fraction alone? The answers to these questions are given in the 2 calculations below.

For purpose of calculation, ultrafiltered diiodotyrosine peptone (described in table 3, preparation V, of the paper by Salter and Pearson, 16) is used. Our figures for the apparent thyroxin iodine were 1 per cent of the total iodine in the diiodotyrosine peptone and 13 per cent in the artificial protein. Prof. G. L. Foster kindly checked these values and obtained 2.1 per cent and 12.5 per cent respectively.

Calculation I. Granting a 2 per cent thyroxin impurity in our diiodotyrosine peptone, the dose of total iodine required to give a standard 0.5 mg. amount of thyroxin iodine daily would be $\frac{0.5}{0.02} = 25$ mg. From such a 25 mg. portion there was obtained a 15 per cent yield in the form of artificial protein, i.e. 3.75 mg. of iodine. Thus, the actual yield obtained was sufficient to treat $\frac{3.75}{0.5} = 7+$ patients instead of 1. Consequently, mere precipitation of a thyroxin impurity could not account for the observed activity obtained by enzymic synthesis.

Calculation II. The standard daily dose of artificial protein used contained 0.5 mg. of total iodine. This is equivalent to $0.5 \times 0.125 = 0.06$ mg. of thyroxin-like iodine. Accordingly, we administered to 3 patients as stated above $\frac{0.06}{0.021} = 3$ mg., or a 6-fold daily dose of diiodotyrosine peptone containing 0.06 mg. of possible thyroxin iodine impurity. These patients showed absolutely no relief.

Furthermore, when thyroxin peptone itself was resorted to and given in a daily dose of $0.5 \times 0.15 = 0.07$ mg. of iodine to a patient with full-blown myxedema, there was practically no effect or at best a debatable one. Consequently, the activity of the artificial protein was much greater than its thyroxin-like fraction alone.

The effect of iodine therapy, interpreted biochemically. These studies also throw light upon the physiological changes induced in the thyroid when iodine is administered to a patient whose thyroid is poor in colloid. The immediate effect is the promotion of colloid storage. This is true whether iodine is given in inorganic (25) or organic form (26). Under such circumstances, large amounts of newly formed thyroid protein (i.e., colloid or thyroglobulin) are stored in the thyroid follicles (1). The present observations suggest that a relatively simple enzymic synthesis may be the mechanism by which this new protein is formed. They suggest, in short, that the therapeutic effect of iodine is indirectly a mass-law phenomenon. The activity of autolytic enzymes in the thyroid gland is evident soon after death: in view of the reversibility of enzyme action, may not these same proteases be responsible for the building up of thyroglobulin during life?

This deduction is based on the hypothesis that when inorganic iodine is administered, it first appears in a chemical form similar to diiodotyrosine peptone. Were this true, diiodotyrosine peptone might be considered as a 'prohormone' (i.e., a precursor) in the same sense that carotene is termed a 'pro-vitamin' with reference to Vitamin A or ergosterol with reference to Vitamin D. It seems that peptic synthesis of the artificial protein may simulate in

vitro a chemical procedure which normally occurs in the living thyroid in the course of the natural manufacture of thyroid protein. Interpreted in this light, the effect of iodine therapy is to favor the synthesis and deposition of hormone, rather than its release.

SUMMARY

About two-thirds of the iodine in thyroglobulin extracted from human glands surgically excised in a non-endemic goitre district (Boston) is not combined as thyroxin. Nevertheless, this 'inactive' diiodotyrosine fraction is a potential source of active hormone. From this peptone an artificial protein can be built up by enzyme action so directed as to reverse the usual digestive process. The artificial protein so obtained resembles natural thyroglobulin in its chemical properties and clinical effects.

The calorigenic effectiveness of the diiodotyrosine peptone fraction of thyroid after appropriate treatment suggests that it represents a chemical precursor which is readily transformed into active thyroid hormone by enzymes within the body.

We are indebted for the human material used in our chemical preparations to the kind cooperation of Dr. Shields Warren of the New England Deaconess Hospital, Boston, Massachusetts.

REFERENCES

1. Marine, D., and W. W. Williams: Arch. Int. Med. **1:** 349. 1908.
2. Oswald, A.: Ztschr. f. physiol. Chem. **27:** 14. 1899.
3. Gutman, A. B., E. M. Benedict, B. Baxter and W. W. Palmer: J. Biol. Chem. **97:** 303. 1932.
4. Harington, C. R., and S. S. Randall: Biochem. J. **23:** 373. 1929.
5. Means, J. H., J. Lerman and W. T. Salter: J. Clin. Investigation **12:** 683. 1933.
6. Lerman, J., and W. T. Salter: Endocrinology **18:** 317. 1934.
7. Salter, W. T.: Am. J. Physiol. **113:** 114. 1935.
8. Boothby, W. M.: Arch. Int. Med. **56:** 37. 1935.
9. Salter, W. T., J. Lerman and J. H. Means: J. Clin. Investigation **12:** 327. 1933.
10. Wormall, A.: J. Exper. Med. **51:** 295. 1930.
11. Hutchison, R.: J. Physiol. **23:** 178. 1898-9.
12. Abelin, I.: Klin. Wchnschr. **13:** 940. 1934.
13. Harington, C. R., and W. T. Salter: Biochem. J. **24:** 456. 1930.
14. Foster, G. L.: J. Biol. Chem. **83:** 345. 1929.
15. Gutman, A. B., E. M. Benedict and W. W. Palmer: Proc. Soc. Exper. Biol. & Med. **29:** 1198. 1932.
16. Salter, W. T., and O. Pearson: J. Biol. Chem. **112:** 579. 1936.
17. Palmer, W. W., D. A. Carson and L. W. Sloan: J. Clin. Investigation **6:** 597. 1928-9.
18. Shorr, E., H. B. Richardson and J. S. Mansfield: Proc. Soc. Exper. Biol. & Med. **32:** 1340. 1935.
19. Palmer, W. W., and J. P. Leland: J. Clin. Investigation **14:** 619. 1935.
20. Harington, C. R., and S. S. Randall: Quart. J. Pharm. & Pharmacol. **2:** 501. 1929.
21. Hutchison, R.: J. Physiol. **20:** 494. 1896.
22. Strouse, S., and C. Voegtlin: J. Pharmacol. & Exper. Therap. **1:** 123. 1909.
23. Thompson, W. O., J. M. Alper, P. K. Thompson and L. F. N. Dickie: J. Clin. Investigation **13:** 29. 1934.
24. Thompson, W. O., P. K. Thompson, S. G. Taylor, III, S. B. Nadler and L. F. N. Dickie: J.A.M.A. **104:** 972. 1935.
25. Plummer, H. S.: J.A.M.A. **80:** 1955. 1923.
26. Harington, C. R.: Proc. Roy. Soc. Med. **26:** 870. 1933.

THE INFLUENCE OF THE INTAKE OF CALCIUM ON THE BLOOD IODINE LEVEL

JUANITA THOMPSON

From the Laboratory of Experimental Neurology, Department of Neurology, New York University College of Medicine

NEW YORK CITY

Our present conception of the association between a relative iodine insufficiency within the body and the initiation of goiter (1, 2) superseded numerous hypothetical explanations. Of the latter, the theory that an exqess of calcium in the drinking water is a goitrogenic factor was advanced as an explanation for the prevalence of thyroid disease in people living on geological formations rich in limestone (3, 4, 5). This hypothesis fell into disrepute due to inadequate experimental confirmation. In recent years, investigation of nutritional problems has revived an interest in the relationship of calcium and goiter. Evidence derived from feeding experiments has been brought forward to show that a relative iodine deficiency and its manifestations in rats are enhanced by excess dietary calcium (6, 7, 8). The reason for such a response is not clear. Accordingly, the present study was undertaken in an attempt to ascertain whether the amount of calcium in the diet influenced the level of iodine in the blood.

In order to establish such a relationship, groups of young rats were placed on specific synthetic diets in which there was a variation in the calcium-iodine ratio. The total blood iodine and serum calcium were determined at definite intervals over a period of 7 months. Should it be found that differences in the amount of calcium in diets of the same iodine content affect the blood iodine level, then one should not overlook the converse relationship when calcium is the constant and iodine the variant.

METHOD OF STUDY

The rats were kept in roomy wire cages with mesh bottoms, not more than 5 animals in a cage. The cages were frequently washed and sterilized; no bedding was used. In order to avoid cross contamination with iodine, the experimental groups were run either at different time intervals or kept in separate and remote quarters.

The basic diet consisted of 76 per cent ground yellow corn, 14 per cent wheat gluten, 6 per cent wheat germ, 1 per cent sodium chloride, 1 per cent 1D Viosterol[1] and distilled water. Tomato juice, 1 cc. per rat per day was added. This food by analysis was found to contain approximately 0.08 gm. of calcium and 0.003 mg. of iodine per 100 gm. The above basic diet was used as well as combinations formed by the addition of calcium carbonate, or potassium iodide or both. The following diets were employed: Group A—

[1] 1D viosterol was obtained by diluting 250D viosterol with a requisite amount of corn oil.

basic diet (low calcium-low iodine); Group B—basic diet plus 3 per cent $CaCo_3$ (high calcium-low iodine); Group C—basic diet plus 1.28 mg. per cent KI (low calcium-adequate[2] iodine); Group D—basic diet plus 1.28 mg. per cent KI plus 3 per cent $CaCO_3$ (high calcium-adequate[2] iodine); Group E—basic diet plus 3.84 mg. per cent KI (low calcium-high iodine); Group F—basic diet plus 3.84 mg. per cent KI plus 3 per cent $CaCO_3$ (high calcium-high iodine). As much food and water as the animals would voluntarily consume was given.

At 1 month of age 540 rats were placed on these various diets. A number were killed at monthly intervals over a period of 7 months. After the desired experimental period had elapsed, the animals were etherized and incompletely exsanguinated by bleeding from the great vessels of the neck. Pooled blood was collected into suitable containers for iodine and calcium estimations. After the blood had clotted, the serum was pipetted off. The calcium content of the serum was determined by the Kramer-Tisdall method (9). The iodine content of the whole blood was estimated by the Perkin method (10). This method has been found to be accurate, with an error of less than 6 per cent.

RESULTS

After the rats had been on the experimental diet for a short time, diverse clinical manifestations developed. The signs were peculiar to certain groups. In animals on low iodine diets (groups A and B) the changes observed have been detailed in previous communications (7, 8) and will be briefly summarized here. In general, the rats presented many of the clinical features of exophthalmic goiter in man, namely, increased excitability, increased activity and food intake, failure to gain in weight, and exophthalmos. These manifestations were more marked in the group receiving additional calcium in the basal diet (group B).

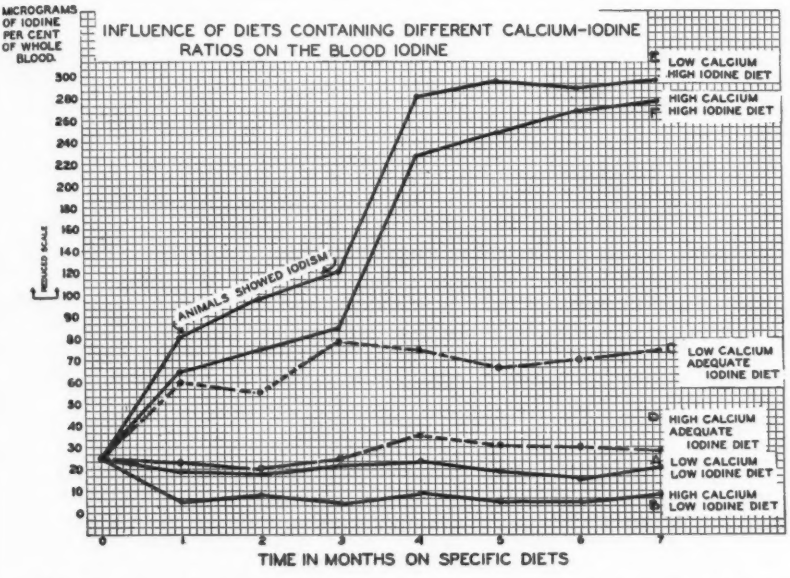
Of considerable interest were the signs shown by the rats on the low calcium-high iodine regimen (group E). During the 4th week, practically all the rats showed excessive lacrimation associated with conjunctival injection and nasal discharge. These characteristics became greatly exaggerated during the 6th week. The eyelids appeared oedematous, conjunctival injection became more intense associated in many cases with engorgement of the corneal vessels. A copious seroexudate overflowed the margins of the lids. The nasal discharge increased in amount and was tinged with blood. It frequently dried about the nostrils forming reddish brown crusts. In addition, there was a change in the appearance of the animals' fur; it became coarse, uneven and a large amount was shed. Together with the above signs, many of the rats developed a mild diarrhoea. The clinical picture presented by the experimental rats was believed to resemble iodism in man.

In a few instances, the condition became acute and death resulted. At autopsy, the most outstanding gross finding was intense engorgement of the gastro-intestinal tract. The survivors began to show clinical improvement dur-

[2] The term 'adequate' was used purely in a differential sense. It is not meant to imply that the addition of 1.28 mg. per cent of KI to a diet is the 'normal' requirement for rats.

ing the 8th week. By the 12th to the 14th week, all manifestations simulating iodism had subsided. Throughout the remainder of the experimental period, the rats showed no clinical changes of note.

The food intake of the above mentioned group E as compared with that of animals receiving a diet of similar iodine content supplemented with 3 per cent $CaCO_3$ (group F) was of interest. During the first month, the consumption of both groups (E and F) was practically the same. Gradually, the food intake of the low-calcium group (E) was voluntarily reduced. At the


MICROGRAMS OF IODINE PER CENT OF WHOLE BLOOD
INFLUENCE OF DIETS CONTAINING DIFFERENT CALCIUM-IODINE RATIOS ON THE BLOOD IODINE
LOW CALCIUM HIGH IODINE DIET
HIGH CALCIUM HIGH IODINE DIET
ANIMALS SHOWED IODISM
REDUCED SCALE
LOW CALCIUM ADEQUATE IODINE DIET
HIGH CALCIUM ADEQUATE IODINE DIET
LOW CALCIUM LOW IODINE DIET
HIGH CALCIUM LOW IODINE DIET
TIME IN MONTHS ON SPECIFIC DIETS

end of the second month, the intake approximated one-half that of the rats receiving additional calcium (group F). This relationship persisted throughout the remainder of the experimental period. During the 5th, 6th and 7th months, the voluntary intake of both groups was considerably reduced over the earlier period.

Rats maintained on the low-calcium, adequate-iodine diet (group C), the high-calcium, adequate-iodine diet (group D) and the high-calcium, high-iodine diet (group F) showed no remarkable clinical findings during the course of the experiment.

The average iodine content of the whole blood expressed in micrograms per cent, taken at monthly intervals from a representative number of the experimental rats in each group has been charted (see graph). It will be seen that: *a)* an increased intake of iodine was reflected in a higher level of iodine in the blood (groups E,F>D,C>A,B); *b)* the addition of calcium to diets containing the same amount of iodine was associated with a relatively lower blood-iodine content (groups B<A; D<C; F<E). This reduction assumed more significance in view of the fact that the voluntary intake of the different

experimental groups on high-calcium regimens was proportionately greater than comparable groups on diets low in calcium.

The length of time on the experimental diets in relation to the level of iodine in the blood was significant. As indicated in the graph, the blood iodine of rats on low-iodine and adequate-iodine diets (groups A,B,C,D) was maintained at a fairly constant level throughout the entire experimental period. In contrast, the time factor was important in the high-iodine groups (E,F). Analysis showed a slight increase in the iodine level from the first to the 3rd months; during the 4th month there was a rapid rise to almost 3 times the former values. In the low-calcium group (E), this high level persisted throughout the remainder of the experimental period. The high-calcium group (F) showed a gradual increase. In connection with the change in the level of blood iodine occurring in the rats on high-iodine diets (groups E,F),

TABLE 1. SERUM CALCIUM VALUES.

Diet	No. of Determinations[1]	Av. Serum Calcium mg.%	Range of Serum Calcium Values mg.%	% of Values within the Range of 9–11 mg.%[2]	% of Values exceeding 11.5 mg.%
Low-calcium, low-iodine (group A)	25	8.5	7.5– 9.5	48	0
Low-calcium, adequate-iodine (group C)	20	7.5	6.2– 8.3	0	0
Low-calcium, high-iodine (group E)	18	7.4	6.2– 8.5	0	0
High-calcium, low-iodine (group B)	21	11.3	9.9–12.5	56	44
High-calcium, adequate-iodine (group D)	35	11.2	9.5–12.5	80	20
High-calcium, high-iodine (group F)	21	10.8	9.5–12.0	86	24

[1] In making the estimations, the pooled serum from 2 rats was used.
[2] 9-11 mg. % has been considered the normal range in rats (11).

it was of interest that the period of greatest gain in weight and food consumption corresponded with the finding of the lower blood-iodine values. With cessation of growth and decreased food intake, the blood iodine increased. Although the height of the blood iodine in the low-calcium group (E) from the 4th to the 7th month was relatively higher than the group on the high-calcium diet (group F), the intake of the rats on low calcium was comparatively greatly diminished. From the present findings, it would appear that beyond certain limits no close relation existed between the iodine consumed and the amount of blood iodine.

The serum calcium from a representative number of animals in each age group was determined. The findings are shown in table 1. Comparative study of the results showed that the serum calcium in rats on low-calcium regimens was slightly lower (1 mg. per cent) in the groups receiving addi-

tional iodine with none presenting normal values, 9-11 mg. per cent being taken as the "norm" (11). The average serum calcium was approximately the same in rats on diets high in calcium. In the groups receiving additional iodine, a smaller percentage gave values slightly increased above the normal. From the above findings, it would appear that there was a tendency toward a lower serum calcium in animals receiving additional iodine in their food.

DISCUSSION

Recent investigations have demonstrated that a greater and more rapid increase in the size of the thyroid gland as well as more marked hyperplasia was initiated in rats through the addition of $CaCO_3$ to a low-iodine diet (6, 7, 8). The response was considered indicative of a relatively greater iodine deficiency within the body. This hypothesis was confirmed by chemical estimations of blood iodine in the present study in rats on low-iodine diets (B<A). Additional evidence is presented to show that the intake of calcium affects the blood iodine. Compared with the blood-iodine values of the low-calcium controls, the blood-iodine level was invariably lower in the animals receiving supplemental calcium in diets either adequate (so-called) or high in iodine (D<C: F<E). In so far as an analogy is permitted, one would conclude that a correlation exists between the hypothesis of iodine deficiency and excess of calcium relative to the incitation of goiter.

Hellwig has reported that the serum calcium of rats on a diet high in calcium and in iodine is reduced by one-half of that with a diet of the same calcium content but low in iodine (12). In the present study, the findings were not so radical. The wide variations found in animals on the same regimen are difficult to explain. In the low-calcium groups where iodine was added to the diets, the serum-calcium values consistently fell below the normal range. In comparative groups on diets of high-calcium content, the addition of iodine lowered the percentage of increased serum-calcium values, whereas the average serum-calcium findings within both the high- and low-calcium groups showed little, if any, difference. As is well known, a great depletion in the calcium reservoirs of the body may take place prior to any demonstrable change in the level of the serum calcium. In some unpublished results, chemical analysis has shown that the calcium content of the bone ash and the fat-free bones is reduced in rats on high-iodine diets in comparison with controls receiving smaller amounts. Therefore, the present trend toward lower serum-calcium values was considered significant.

In man, the administration of iodine preparations is frequently associated with the development of iodism (13, 14, 15). The dosage giving rise to such a condition varies with the individual and the compound used. Cure may occur spontaneously or be effected by reducing or increasing the dose in patients receiving KI. Numerous ingenious hypotheses have been advanced to explain the mechanism involved but none have been adequately established. The signs of a condition resembling iodism in rats on the low-calcium, high-iodine diet (group E) were manifest. Their absence in the high-calcium group (F) indicated that calcium acted as a preventative. This

experimental finding lends credence to the clinical observations of Velden who reported that the catarrhal phenomena of iodism could be suppressed by large doses of calcium lactate (16).

If the prevalent view that iodism is associated with an increased elimination of iodine by the tears, secretions of the respiratory mucous membranes and skin be true, it follows that an excess of iodine in the blood is likely. So far as I am aware, this assumption has not been confirmed by chemical estimations of the blood iodine before, during and following an attack. For this reason, it was thought that some insight into the problem might be gained by an analysis of the present data. As has been detailed above, signs resembling iodism developed during the 4th week in the group of rats on the low-calcium, high-iodine diet (group E). Up to the 6th week, the condition became progressively more acute. Spontaneous cure was effected by the end of the 14th week. Review of the blood-iodine values showed that the level of iodine in the blood was relatively much lower during the period when the signs of iodism were manifested. Furthermore, practically coincident with the spontaneous remission, the blood-iodine content was rapidly increasing. This finding suggested the possibility of a divergence from some of the usual paths of elimination such as the tears and secretions of the respiratory tract. If such were true, the clearing up of iodism might be in part explained. However, when one considers that rats receiving a diet of the same iodine content but high in calcium (group F) showed no unfavorable clinical reactions despite the fact that their blood iodine at a slightly later period reached the same concentration and also showed a similar marked increase compared with that of the low-calcium group (E), the fallacy of the above explanation will be seen. The experimental evidence indicated that iodine induces the clinical syndrome of iodism only under special conditions and that the concentration of iodine in the blood alone is not the determining factor. In the present experiments, the accessory factor would appear to be a deficiency of calcium.

SUMMARY

Five hundred and forty rats on specific synthetic diets in which there was a variation in the calcium-iodine ratio were studied over a period of 7 months. The results of chemical analysis have shown that the amount of calcium in the diet influenced the level of iodine in the blood. In animals on diets containing the same amount of iodine, the blood-iodine level was comparatively lower in the groups receiving additional calcium than in the controls. On high-iodine diets, there did not appear to be any close relation between the amount of iodine consumed and the blood-iodine level (time was an important factor). In contrast, the average serum-calcium level was not markedly affected by varying the dietary iodine.

Disturbing the calcium-iodine ratio of the diet beyond certain limits was associated with the development of diverse clinical manifestations peculiar to certain experimental groups. The rats on low-iodine diets showed many of the clinical changes found in human cases of exophthalmic goiter. Animals

maintained on a diet low in calcium and high in iodine developed signs resembling iodism.

The experimental findings relative to iodism are considered to indicate that iodine induces the syndrome only under special conditions; the concentration of iodine in the blood is not the determining factor. The intake of calcium has an important influence, in that an excess in the diet acts as a prophylactic whereas a deficiency favors the development of iodism.

REFERENCES

1. Marine, D., C. H. Lenhart, D. P. Kimball, and J. M. Rogoff: The Prevention of Simple Goitre, Bull. Western Reserve Univ., No. 26, 1923.
2. McClendon, J. F., and A. Williams: Proc. Soc. Exper. Biol. & Med. **20:** 286. 1922-23.
3. Berry, J.: Diseases of the Thyroid Gland, P. Blakiston's Son and Co., Philadelphia, 1901.
4. Berry, J.: Lancet **1:** 269. 1926.
5. Orr, J. B., and I. Leitch: Iodine in Nutrition, Med. Res. Council, Sp. Rep. Series, No. 123, London, H. M. Stationery Office, 1929.
6. Thompson, J.: J. Nutrition **5:** 359. 1932.
7. Thompson, J.: Arch. Path. **16:** 211. 1933.
8. Thompson, J.: Endocrinology **17:** 537. 1933.
9. Cole, S. W.: Practical Physiological Chemistry, p. 437, W. Heffer and Sons, Ltd., Cambridge, 1928.
10. Perkin, H. J.: Biochem. J. **27:** 1078. 1933.
11. Donaldson, N. H.: The Rat, Memoirs of the Wistar Institute of Anatomy and Biology, No. 6, Philadelphia, 1924.
12. Hellwig, C. A.: Arch. Path. **19:** 364. 1935.
13. Cushny, A. R.: Pharmacology and Therapeutics, 9th ed., Edmunds, Gunn, Lea and Febiger, Philadelphia, 1928.
14. Sollmann, T.: Manual of Pharmacology, 3rd ed., W. B. Saunders Co., Philadelphia and London, 1930.
15. Wood, H. C., and C. H. LaWall: U. S. Dispensary, 21st ed., J. B. Lippincott Co., Philadelphia, 1926.
16. Velden, R. Van den.: Therap. Monatsh. **27:** 685. 1913.

SUBCLINICAL HYPOTHYROIDISM IN CHILDREN[1]

MATTHEW MOLITCH AND SAM POLIAKOFF
Department of Neurology, University of Pennsylvania
PHILADELPHIA, PENNSYLVANIA
and the New Jersey State Home for Boys
JAMESBURG, NEW JERSEY

The inmate population of the New Jersey State Home for Boys was studied to determine the incidence of mild cases of hypothyroidism. The boys ranged in age between 8 and 17, the majority being about 14 years. The entire population of over 500 boys was skiagraphed and those with delayed carpal development were studied in more detail. Total serum cholesterol determinations were made on the entire group and norms were developed. Those with retarded osseous development and those with high cholesterol were given basal metabolism tests. The findings were then correlated with psychological data, behavior and school achievement.

OBSERVATIONS

Roentgenographic studies. The carpal bones of 514 boys were studied and 54, or 10.5 per cent, were found to have retarded development of from 2 to 4 years. Table 1 gives the distribution of the cases; 24 of these, with more than 3 years retardation, were found to have no endocrine dysfunction which would make the hypothyroidism a secondary or associated phenomenon. All the joints of the 54 boys were studied and compared with the norms published by Shelton (1).

Cholesterol studies. Serum total cholesterol values were determined on blood specimens from fasting subjects using Sackett's (2) modification of Bloor's method. A more stable color development was used as suggested by Reinhold (3). In this technic 2 cc. of acetic anhydride and 0.1 cc. of concentrated H_2SO_4 were added to both the specimens and the standard. The contents were mixed and allowed to stand at 30°c. for 15 minutes in the light to be used in making the readings. The final readings were made through a red filter. We found that the standard began to show deterioration after 20 minutes so that the color of 1 standard and of about 15 'unknowns' was developed at one time. We were able to get consistent results with the above technic and it was especially practical as elaborate equipment was not necessary. Check determinations were made by John G. Reinhold of the Laboratories of the Philadelphia General Hospital.

Determinations were made on over 500 boys, both normal and abnormal. Of this number 284 were normal from an endocrine standpoint and were used as controls. The remainder were boys who had some obvious endocrine dysfunction, or were from groups who had access to a higher fat diet. Table 2 gives the normal distribution and table 3 gives the statistical analysis. There

[1] Read before the Twentieth Annual Meeting of the Association for the Study of Internal Secretions, Kansas City, May 12, 1936.

TABLE 1. ROENTGENOGRAPHIC STUDIES.

No. of Boys Skiagraphed (Carpals)	Normal Findings	Delayed Carpal Development	Further Studies on Those with Delayed Carpal development		
			Years retarded		
			2	3	4
514	460	54	22	21	11
Percentage	89.5	10.5	40.7 of 54	38.9 of 54	20.4 of 54
			4.3 of 514	4.1 of 514	2.1 of 514

was little difference between the white and colored boys and 85 per cent of the controls ranged between 100-160 mg., while the entire range was between 80 and 204 mg. per 100 cc. Our range is comparable with that of Rothbart (4) who found it in 98 children to be between 120 and 170 mg. Table 4 gives the cholesterol findings in the 24 boys specially studied; they all fell within the normal range. It might be added that only 3 were in the lowest quartile while 9 were at or above the upper quartile.

Basal metabolism. Basal metabolic rates were determined on all the boys with retarded osseous development and with high cholesterol levels. The procedure and norms used were those published by Molitch and Cousins (5). We were able to get excellent coöperation from the boys and, as has been published elsewhere (5), we were able to get determinations that agreed within 4 per cent on successive days. The Sanborn 'Motor-Grafic' machine was used and every boy was admitted to the institution hospital the evening before to insure basal conditions in the morning.

Table 4 gives the results of this study. Our findings confirm those of Rothbart (4), who found that there was no relationship between basal metabolism and the level of serum cholesterol. Of the 24 children with 3 or more years osseous retardation, 7 had a mildly deficient oxygen-consumption rate while the remainder were on the positive side. It then appears that there is no correlation between osseous retardation and basal metabolism, while the serum cholesterol seems to be higher but within the normal range.

TABLE 2. DISTRIBUTION OF SERUM CHOLESTEROL VALUES WITH AGE IN NORMAL BOYS.

Age (years)	No.	Range of Cholesterol Values, Mg. per cent					
		81–100	101–120	121–140	141–160	161–180	181–204
8	1			1			
9	3		1	2			
10	7		4	3			
11	12	1	2	6	2		1
12	24	1	4	8	10		1
13	34	1	11	12	7	3	
14	40	4	13	14	5	4	
15	92	9	28	24	21	9	1
16	61	2	23	16	16	4	
17	6		1	2	2	1	
18	4		2	1		1	
Total	284	18	89	89	63	22	3
Percentage	100.0	6.3	31.3	31.3	22.3	7.7	1.1

TABLE 3. STATISTICAL ANALYSIS OF CHOLESTEROL DISTRIBUTION.

	Number of Boys	Lower Quartile mg. %	Median mg. %	Upper Quartile mg. %	Total Cholesterol mg.	Average Cholesterol mg. %
Total	284	114.3	127.5	146.0	37112	130.7
White	164	114.8	129.0	146.9	21643	132.0
Colored	120	114.3	124.7	144.3	15469	128.9

Table 5 gives the anthropometric data. It is seen that 6 were below the minimum while none were above the maximum in height. Only 1 was below the minimum in weight, the remainder were at about the optimum while 3 were above the maximum. Eight of the boys showed little or no evidence of secondary sexual development. In more than half the cases the skin seemed dry and the hair brittle. Not one boy had a secondary anemia and only one gave a history of constipation.

Intelligence.—The findings of general mental level for this group were made by A. K. Eccles and Marian Derrick. Upon admission each of these inmates was given a psychological examination including one of the following tests: Stanford revision of the Binet; Kuhlmann-Anderson; Morgan's mental test A or B; also the mirror drawing test, dynamometer for strength of grip, and the Witmer form board. In addition to these, 1 or more, usually 3, of the following performance tests were given: Healy picture completion II; Porteus maze; Stenquist assembly I; Stenquist mechanical aptitude I; Knox cube.

We did not consider it practicable to use intelligence quotients because of the differences in the tests employed and the consequent incomparability of the quotients obtained. Other factors were the differences in nationality and color and the debatable question as to whether intelligence quotients are sufficiently constant to warrant com-

TABLE 4. LABORATORY DATA.

Case	Age years and Months	Surface Area Sq. M.	Basal Metabolism Cal/sq. M./Hr.		Blood Cholesterol Mg. per 100 cc.
			Actual	Normal[1]	
W.R.	13–2	1.28	38.4	42.8	125
A.J.	13–11	1.50	39.0	42.8	116
M.R.	15–3	1.24	37.8	41.1	130
C.V.	13–10	1.27	40.2	42.8	144
H.H.	12–11	1.27	39.6	41.9	112
K.F.	13–8	1.24	42.2	42.8	119
R.G.	15–5	1.42	40.7	41.1	103
R.C.	14–10	1.38	40.9	40.7	146
M.F.	14–2	1.41	41.1	40.7	134
B.D.	16–7	1.36	41.6	41.0	124
S.N.	12–2	1.23	42.8	41.9	177
P.J.	14–9	1.40	42.2	40.7	157
M.R.	14–6	1.46	42.3	40.7	146
M.L.	15–11	1.38	43.1	41.1	157
T.S.	15–8	1.41	43.3	41.1	172
F.M.	14–9	1.46	50.0	40.7	127
B.G.	14–8	1.17	43.4	40.7	167
D.W.	14–3	1.32	43.4	40.7	146
C.J.	10–1	0.99	48.3	43.1	145
B.W.	15–0	1.36	45.9	40.7	128
L.F.	12–10	1.18	47.8	41.9	160
S.B.	14–5	1.11	48.6	40.7	107
H.D.	14–3	1.33	48.7	40.7	134

[1] Norms according to Molitch and Cousins.

parison in this type of data for different ages, and still further because of the uncertainty of the upper life-age limit for calculating quotients.

We confirmed Rothbart's (4) findings that there is no correlation between serum cholesterol and mental level. Molitch and Eccles (6) and later Rothbart (4) found a negative correlation between the oxygen consumption rate and the mental level. Of the 24 boys with retarded osseous development, 8 or 33.3

TABLE 5. ANTHROPOMETRIC DATA.[1]

Case	Color	Age Years and Months	Height (inches)			Weight (pounds)			Bone Retardation[2] (years)
			Actual	Min.	Max.	Actual	Min.	Max.	
C.J.	W	10–1	52.3	51.3	55.0	58	57.0	71.6	3
S.N.	W	12–2	57.8	55.2	59.0	87	69.4	87.2	3
L.F.	W	12–10	55.5	56.0	60.0	75	72.7	91.3	4
H.H.	B	12–11	58.0	56.0	60.0	88	72.7	91.3	3
W.R.	B	13–2	58.5	56.9	60.9	90	75.9	95.7	3
K.F.	W	13–8	59.0	57.8	61.8	80	79.3	100.3	3
C.F.	W	13–10	57.5	57.8	61.8	90	79.3	100.3	3
A.J.	W	13–11	62.5	57.8	61.8	115	79.3	100.3	3
M.F.	W	14–2	60.3	58.6	62.8	100	81.1	102.9	3
D.W.	W	14–3	58.3	58.6	62.8	93	81.1	102.9	3
H.D.	B	14–3	60.5	58.6	62.8	91	81.1	102.9	3
S.B.	B	14–5	54.8	58.6	62.8	74	81.1	102.9	3
M.R.	B	14–6	60.3	59.5	63.7	115	85.0	108.0	3
B.C.	B	14–8	56.8	59.5	63.7	73	85.0	108.0	3
F.M.	W	14–9	62.5	59.5	63.7	105	85.0	108.0	3
P.J.	W	14–9	61.0	59.5	63.7	101	85.0	108.0	3
R.C.	B	14–10	60.3	59.5	63.7	97	85.0	108.0	3
B.W.	B	15–0	60.3	60.3	64.5	98	89.4	113.4	3
M.R.	W	15–3	55.3	60.3	64.5	90	89.4	113.4	4
R.G.	B	15–5	60.0	60.3	64.5	104	89.4	113.4	3
T.S.	W	15–8	59.5	61.1	65.3	106	91.6	116.2	3
M.L.	W	15–11	60.5	61.1	65.3	96	91.6	116.2	4
J.E.	W	16–4	65.0	61.8	66.2	128	96.0	122.0	4
B.D.	B	16–7	61.3	62.5	66.9	96	98.4	125.0	4

[1] Height and weight minimum and maximum data (normal limits) according to Engelbach.
[2] Bone retardation derived from Shelton's norms.

per cent were average normal, 7 or 29.2 per cent were inferior normal, while 9 or 37.5 per cent were feebleminded. The average for the population as a whole was 28 per cent average, 39 per cent inferior and 33 per cent subnormal or feebleminded. The group is too small to permit a generalization, and an increase in both the higher and lower mental levels at the expense of the inferior normals was noted. In our study it may be concluded that mental retardation is not an important manifestation in subclinical hypothyroidism.

School achievements. A Stanford achievement test was given to each boy and only 3 made normal or above-normal grades for their age. Two made no score, except in arithmetic, and the remainder were retarded from 2 to 6 years. This is also true for the remainder of the population and is therefore not distinctive of this group. All but 2 boys were chronic truants and offered behavior problems before commitment. This is higher than the incidence for the remainder of the population.

Behavior. Three boys were committed because of chronically running away from home; 1 for a sex offense; 1 for assault, and the remainder for stealing. This type of record is also true for the general population. Only 3 of the group

fell into what might be called a hypoactive category while the rest were hyperactive in varying degrees. One boy gave way to very serious temper tantrums and when thwarted would bang his head against a stone wall. In addition 3 more boys offered institutional problems while the remainder were considered as average in behavior and adjustment. As a group they were more stable than our boys with cryptorchidism (7) or those with pituitary dysfunctions (8). Although these boys, as a group, were not recalcitrant yet individually we find them described in such negative terms as: immature, suggestible, inadequate, unstable, distractible, emotional, quick-tempered, 'sneaky,' having inferiority complexes, negativistic. Some are described positively as polite, coöperative and good workers.

It is difficult to set up a normal behavior pattern for a group in an institution where almost all the boys were committed because of overt acts. There is nothing distinctive about this group which would differentiate them from the standpoint of behavior as do impulsive acts in chronic post-encephalitic patients (9).

DISCUSSION

Questionaires concerning hypothyroidism in children were sent to a group of outstanding endocrinologists and their replies were compiled under the headings of laboratory, clinical and behavior findings. From the laboratory standpoint, all respondents were in agreement that the most important and consistent finding in hypothyroidism is retarded osseous development. Several men prefer to make basal metabolism tests in the older children and roentgen ray studies in the younger. Basal metabolism studies were mentioned by all, but almost everyone gave warning about the unreliability of the test in younger children, inadequate standards, and their frequent lack of correlation with clinical findings. It seems that the basal metabolism is taken as a routine procedure but that little importance is given the results except when they comport with the clinical picture. Our findings certainly show that the basal metabolism test is not in itself an important datum.

More than half the group replying to our questionaire mentioned blood cholesterol and several did not qualify their answer. The group seemed to be in agreement that the results are variable and not specific. Our findings were not spectacular but there seemed to be a tendency towards high normals in the children with osseous retardation.

Several mentioned that a secondary anemia may be present but this was not evident in our group. One man makes a glucose tolerance test to rule out hypopituitarism with associated hypothyroidism, while another reports that he gets valuable information from fasting blood sugar tests. One mentioned that a scanty urine with a low total nitrogen may be present, and that the creatine output in the urine should receive more study.

In the clinical approach more than half the group placed special emphasis on a history of delayed walking, talking, and teething during infancy. One man pointed out the fact that a history of a rapid gain in mother's weight during pregnancy and the birth of a child over 8½ pounds, might be of help in the diagnosis.

In the physical examination the most frequently mentioned finding was a

dry skin and brittle hair. The skin might even be ichthyotic and ofttimes a dermatitis or dermatosis may be present. Next in frequency were overweight, constipation and stunted growth. Other signs or symptoms mentioned were: delay in second dentition with teeth that are thin, short, brittle and with a tendency to decay; skin sensitive to cold, with cold extremities; lack of vigor; genital hypoplasia; nuchal distribution of fat; abnormality of body growth with a short lower measurement and a span less than the total height.

From the standpoint of behavior there seems to be more of a difference of opinion. Half of the group considered behavior so variable as to be of little value as an aid in diagnoses. It appears that a child with hypothyroidism may reveal one of two pictures. He may be dull, apathetic, stupid, sluggish, weak, weary and be mentally retarded. His school work may be poor and he may be unable to keep up in competitive sports. On the other hand, he may be irritable, unmanageable, stubborn, fretful, sleep poorly, be emotionally unstable, and have a capricious appetite. Finally, more than half the group replied that the most important test of all was the response of the child to small doses of thyroid gland substance.

SUMMARY AND CONCLUSIONS

Roentgen ray and blood serum cholesterol studies were made on over 500 boys committed to a corrective institution. Basal metabolism tests were made on those boys with retarded osseous development and on those with high serum cholesterol findings. A small group of boys with retarded osseous development and without other endocrine dysfunctions were studied in detail and correlations were made with their mental level, school achievement and behavior. The results of our study were checked against the opinions of 11 outstanding endocrinologists that were obtained, by the questionaire method. The results of our study in consonance with the opinions of others indicates that osseous retardation is the most consistent finding in hypothyroidism in children. Basal metabolism and serum cholesterol findings are of little aid in the diagnosis in children, because of variability and lack of consistent relationship to the clinical pictures. In the clinical picture only dryness of the skin and the brittleness of the hair were consistently found. A history of overweight at birth and a delay in development such as teething, walking and talking, is of corroborative significance. The intelligence is not a reliable criterion; some hypothyroid children are bright and some retarded. The behavior was found to be either hypoactive or hyperactive hence of little aid in the diagnosis.

Subclinical types of hypothyroidism may be recognized by the osseous retardation, as revealed by x-ray, and by the favorable reaction of the patient to replacement therapy with thyroid gland substance.

REFERENCES

1. Shelton, E. K.: J.A.M.A. **96:** 759. 1931.
2. Sackett, G. E.: J. Biol. Chem. **64:** 203. 1925.
3. Reinhold, J. G.: Personal communication.
4. Rothbart, H. B.: Am. J. Dis. Child. **49:** 672. 1935.
5. Molitch, M. and R. F. Cousins: J. Nutrition **8:** 247. 1934.
6. Molitch, M. and A. K. Eccles: J. Juvenile Research **18:** 135. 1934.
7. Molitch, M.: In Press.
8. Molitch, M. and S. Poliakoff: Am. J. Orthopsychiat. **6:** 125. 1936.
9. Molitch, M.: Am. J. Psychiat. **91:** 843. 1935.

NITROGEN AND CREATINE METABOLISM IN RELATION TO ENVIRONMENTAL TEMPERATURE AND THYROID FUNCTION[1]

M. BODANSKY AND VIRGINIA B. DUFF
WITH THE TECHNICAL ASSISTANCE OF C. M. AGRESS, C. L. HERRMANN AND KATHERINE R. CAMPBELL
From the Laboratories of the John Sealy Hospital and the Department of Pathological Chemistry, University of Texas School of Medicine
GALVESTON, TEXAS

Increased metabolism, a normal response to exposure to cold, is associated with stimulation of thyroid activity, as evidenced partly by hyperplasia of the gland and loss of colloid. These changes may be prevented by the administration of thyroid or thyroxine (1) and somewhat less regularly by iodide (2). In untreated rats kept at low temperatures the augmented metabolism may be related to increased secretion of hormone, while in those treated with thyroid substance it is presumably dependent on the exogenous supply of hormone, inasmuch as the activity of the gland itself is conspicuously depressed (1). This, combined with the augmented hormone requirement, may explain, in part, the increased tolerance to thyroid and thyroxine of rats exposed to a low thermal environment.

Rats have been found to survive long periods of exposure to a temperature of 3-5°C. on doses of thyroid and thyroxine which at higher temperatures (22-30°C.) caused death in a few days. The marked toxicity of thyroid substance at high temperatures (33-35°C) has also been observed in rabbits by Draize (3), who with Tatum (4) applied this property in assaying the biological potency of various thyroid preparations.

To illustrate the resistance at low temperatures, one rat (weight 165 gm.), kept in a cold room, received 2 mg. of crystalline thyroxine (Hoffmann-LaRoche) daily for 30 days, during which time there was no change in weight except for an initial loss which was subsequently regained. Another rat survived a 99-day experimental period of continued exposure to a temperature of 3-5°C., during which time it consumed 90 gm. of desiccated thyroid (Lilly), yet gained 67 gm. in weight. At the conclusion of the experiment, the kidneys of this rat weighed 3.896 gm., which, compared to the standard data in Donaldson's tables (5), as well as with normal data obtained in this laboratory, represents an increase of about 82 per cent. The heart (ventricles) weighed 1.22 gm., or approximately 70 per cent above normal. According to Smith and MacKay (6), the change in heart weight due to thyroid feeding is in the nature of a simple work hypertrophy of the myocardium. As regards the increased renal weight of hyperthyroid rats, MacKay and MacKay (7) have observed that it is greater than can be accounted for by the increase in protein intake incident to the augmented food consumption.

[1] This work was aided by a grant from the National Research Council.

Similar observations led us to investigate in more detail the effects of hyperthyroidism and of prolonged exposure to cold on nitrogen metabolism. While certain facts concerning the influence of cold on the nitrogen output and of the effects of hyperthyroidism and thyroid administration on nitrogen and creatine metabolism are generally known, it seemed desirable in pursuing the problem of the relation of the thyroid to muscle metabolism to obtain additional information on the subject.

METHODS AND RESULTS

In figure 1 are represented graphically the data obtained in an experiment involving the use of 4 rats (male, litter-mates). At the beginning of the

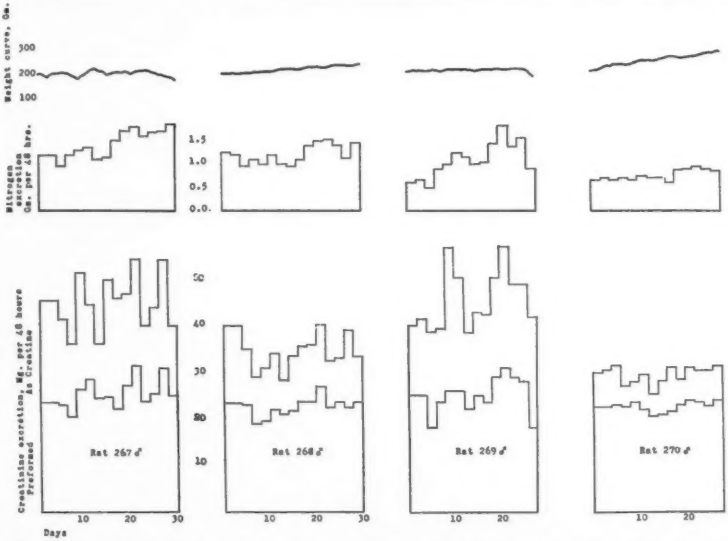


Fig. 1. Rats 267 and 268 were kept at a temperature of 3-5°C. Rat 267 received daily subcutaneous injections of thyroxine, 2 mg., while rat 268 served as control. Rats 269 and 270, litter-mates of the first 2 rats, were kept at room temperature (maximum variation 16-23°C.) Rat 269 received 2 mg. of thyroxine daily. Following a 2-day preliminary period in the metabolism cages, collection of urine was begun and continued for the duration of the experiment, analyses being carried out on 48-hour specimens. The charts represent the 48-hour levels of excretion of total nitrogen, creatine and creatinine.

observations each weighed approximately 200 gm. Each was placed in a separate metabolism cage of the type used in another study (8). The diet was essentially creatine-free, having the following composition: whole wheat flour, 1 part; corn meal, 1 part; dried milk, 1 part; calcium carbonate, 2 per cent; sodium chloride, 1 per cent; brewers' yeast, 3 per cent; and cod liver oil. Rats 267 and 268 were kept in a cold room (temperature 4°C. $\pm$1) for a period of 30 days. Rat 267 received a daily injection of 2 mg. of thyroxine. Rats 269 and 270 were kept at room temperature (maximum variation during month was 16-23°C.). The former received 2 mg. of thyroxine daily. Thus rat 268 served as the normal control in the cold room, while rat 270 was the normal control at room temperature. Rat 269 became moribund on the 29th day and therefore the experiment was discontinued. During the first 28 days of observation, the total nitrogen excretion of rat 270 was 10.57 gm., while rat 269 excreted 15.73 gm.

For the same period of 28 days rat 268 excreted 16.78 gm. and rat 267, 19.17 gm.

It is instructive to correlate these values for nitrogen excretion with the weights of the kidneys. For rat 267, this was 3.2 gm. Based on initial body weight, the kidneys therefore weighed 195 per cent of normal, or somewhat more when computed on the basis of final body weight. For rat 268, the weight (2.44 gm.) was 120 per cent of normal. The kidneys of rat 269 weighed 3.59 or 219 per cent of normal. The renal weight of control rat 270 agreed with the standard value given by Donaldson (5). From these results it would seem that for the thyroxine-treated rat at room temperature, the increased renal weight was proportionately greater than the increase in nitrogen output. For the

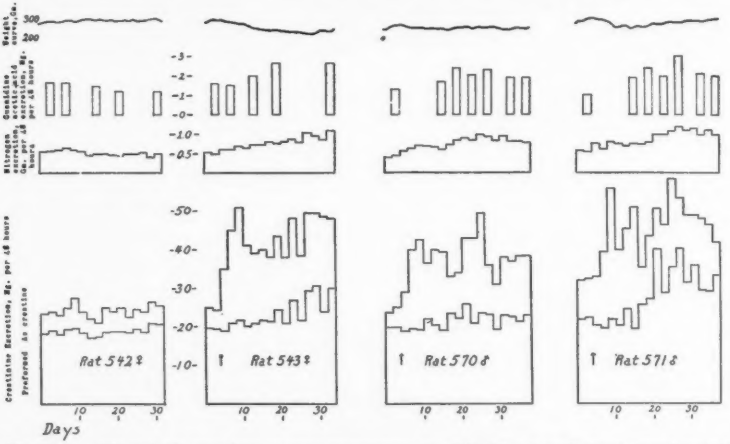


Fig. 2. Rats 542 and 543 were kept at room temperature, 22-25°C. After 2 preliminary control periods of 48 hours each, injections of thyroxine (1 mg. daily, reduced to 0.5 mg. after 10 days) were begun in rat 543 as indicated by the arrow. Rat 542 continued as the normal control. Following 2 metabolism periods at room temperature, rats 570 and 571 were transferred to the cold room, as indicated by the arrows. The injections of thyroxine were begun in rat 571 the same day, the daily dose being reduced from 0.5 mg. to 0.25 mg. on the 27th day of the experiment.

thyroxine-treated rat in the refrigerator, the agreement was somewhat better (renal weight +95 per cent; nitrogen metabolism +81 per cent), while for the normal control in the cold room the relation was reversed (renal weight +20 per cent, nitrogen metabolism +60 per cent).

The total creatinine excreted by rat 270 was 414 mg., of which 100 mg. was in the form of creatine. The relative constancy of the creatinine metabolism of this animal throughout the experimental period, despite the increase in weight, may perhaps be explained on the assumption that the gain was largely of body fat, rather than of muscle. For the same period thyroxine-treated rat 269 excreted 339 mg. of creatinine and 300 mg. of creatine; rat 267 (thyroxine-treated in the cold room) excreted 353 mg. of creatinine and 285 mg. of creatine, while rate 268 (control in cold room) excreted 312 mg. of creatinine and 176 mg. of creatine. From these data it would seem that the output of creatinine was relatively unaffected by the administration of thyroxine, or by exposure to cold, while the creatinuria was greatly augmented (compare, however, with the data charted in fig. 2).

The creatine excretion may be further correlated with the changes in tissue

creatine. Analysis of control rat 270 gave the following values (mg. per 100 gm.): myocardium, 188; muscle, 486; testes, 319. In marked contrast were the following results for thyroxine treated rat 269: myocardium, 87.3; muscle, 358; testes, 333. For the control rat in the refrigerator (268), the figures were: myocardium, 205; muscle, 529; testes, 314. The thyroxine-treated rat in the refrigerator (267) yielded the following data: myocardium, 134; muscle, 412; testes, 426. It is thus seen that the extra creatine excreted by the refrigerator control did not result in a lowering of the creatine content of the tissues, but on the contrary the concentrations were maintained at high normal. It may be pointed out, however, that in poorly nourished rats, prolonged exposure to cold

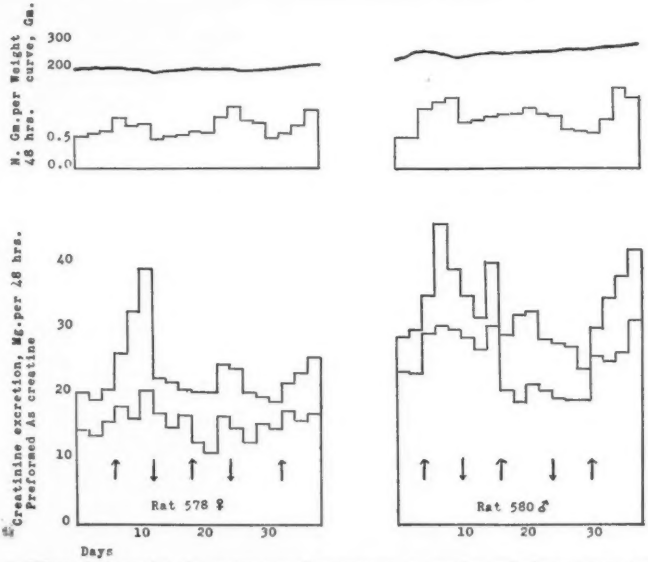


Fig. 3. Effect of alternating the environmental temperature on creatine and nitrogen excretion. Upward pointing arrows denote transfer to cold room (3-5°C.); downward pointing arrows denote return to room temperature.

usually led to a diminution of the creatine concentration of heart and muscle to low normal, or even subnormal values. The results for rats 267 and 269 are typical of many similar data which indicate that at low temperatures depletion of creatine from skeletal muscle and myocardium of the well-nourished, thyrotoxic rat occurs somewhat less rapidly than at moderate to high temperatures.

From the charts in figure 1 it will be further observed that the 48-hour creatine + creatinine excretion of the thyroxine-treated rats and the refrigerator control varied within wide limits. These fluctuations were a cause of much concern and perplexity and were first attributed to possible faults in technique, unequal urine collections, or other unsuspected errors. But as greater uniformity was not obtained even though the work was repeated many times, it was finally concluded that these variations were perhaps inherent in the experimental conditions. There is justification for assuming that the relative constancy of creatinine excretion in the normal rat, as in man, reflects a compara-

tively steady state of endogenous metabolism. When, as in the case of these experiments, the metabolism was raised to an abnormal level by the administration of thyroxine, exposure to cold, or both, the normal relations and regulatory mechanisms were conceivably affected. To the examples of physiological homeostasis cited by Cannon (9), such as the maintenance of uniform basal metabolism, body temperature, hydrogen ion and glucose concentrations of the

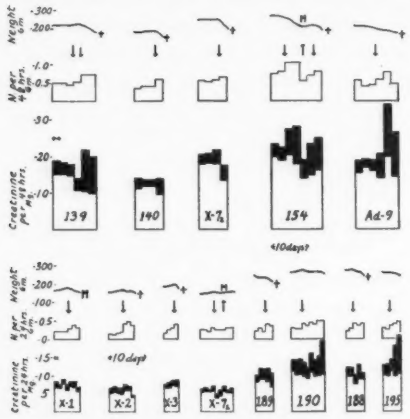


Fig. 4. Metabolism charts of thyroparathyroidectomized rats and their controls. Rats X-1, X-2, X-3 (females) were operated upon at 93 days and transferred to the cold room 5-8 days later. Charts $X\text{-}7_1$ and $X\text{-}7_2$ represent the same rat (female). It was operated upon at 66 days and exposed to cold 11 days later. It became moribund (M) on the third day of exposure, was returned to room temperature and recovered. The test was repeated 6 months later, with the results indicated on the chart $X\text{-}7_2$. Rats 139 and 140 (males) were thyroparathyroidectomized at 31 days and tested 4 months later. Rat 154 (male) was operated upon at 3 months and tested 16 days later. Rats 188 and 189 (males) were thyroparathyroidectomized at 30 days and were tested in the refrigerator 108 days later. Rats 190 and 195 (also males) were their normal, litter-mate controls. Ad-9 was adrenalectomized at 3 months. Renal decapsulation was performed 2 months later, the rat being transferred to the cold room 7 days after the second operation. Downward pointing arrows denote transfer to cold room; upward pointing arrows, return to room temperature. The lower row of charts represent metabolism experiments in which analyses were carried out on 24-hour specimens; in upper row, 48-hour collections were made as in other experiments.

blood may reasonably be added creatine metabolism and accordingly the fluctuations in excretion under the experimental circumstances which have been described may perhaps be considered to represent an unsteady state of endogenous metabolism; in short a condition of disturbed homeostasis.

Guanidine acetic acid. Of the many compounds that have been suggested as precursors or metabolic intermediates of creatine, the evidence points more clearly to guanidine acetic acid than to any other substance (10). It therefore seemed of interest, in connection with these experiments to determine whether the augmented creatine metabolism was in any way related to the excretion of this constituent. For its estimation Weber's method (11) was used. Weber has been able to recover 85 ± 5 per cent of added guanidine acetic acid in urine. In our hands the recoveries have been somewhat lower, approximately 80 per cent, but we have substantiated Weber's claim as to the specificity of this application of the Sakaguchi reaction (12) and are convinced of the value of the results, despite the present imperfection of the method.

In control rat 542 (fig. 2) the 48-hour excretion of guanidine acetic acid varied from 1.2 to 1.7 mg. The excretion of rat 543 during the control period

was 1.6 mg., but increased to 2.6 mg. after the injections of thyroxine (1 mg. daily) were begun. The effect of thyroxine on creatine was prompt and, as in other experiments, the increased excretion was maintained throughout the period of observation, 34 days. In this respect our results differ from those of Pugsley, Anderson and Collip (13), who found that the increased excretion of creatine produced in rats by the administration of desiccated thyroid, or anterior pituitary extract containing thyrotropic hormone, was not sustained indefinitely but gradually diminished after a period of 12 days. Except for the fluctuations previously discussed, reduction in the output of creatine and creatinine in hyperthyroid rats occurred only when they became sick, or semimoribund. This is illustrated by the terminal break in the level of excretion of rat 269 (fig. 1).

Exposure of rat 570 to cold was accompanied by an increase from a normal excretion of 1.3 mg. to a maximum of 2.4 mg., while in rat 571 (thyroxine-treated in the cold room) the increase was even more (from a control value of 1 mg. to 3 mg.). From the charts in figure 2 it would seem that the excretion of guanidine acetic acid was more or less parallel to the level of the endogenous (creatinine), if not to the total protein, metabolism. However, work now in progress suggests that there is perhaps an even closer connection to thyroid function. It has been found that the guanidine acetic acid excretion of thyroparathyroidectomized rats, which is often negligible, is uniformly low both with respect to the absolute amount excreted and in relation to the nitrogen output.

Nature of the Metabolic Response to Cold. Referring again to figure 2, it will be noted that the response to cold was prompt, the creatine and nitrogen elimination being unmistakably increased by the second 48-hour period of exposure. This observation suggested that if this response is associated with stimulation of the thyroid, it should be absent in the thyroidectomized rat. Then too the question arose as to the constancy of the response in the normal rat and its recurrence when the thermal environment is alternated. The answer to the last of these questions is to be found in the charts of figure 3. Rats 578 and 581 were moved in and out of the cold room at intervals of 6 or more days, as indicated. The first exposure to cold produced the typical response but the results of subsequent exposures, though occasionally normal in some of the animals that have been observed, were more often irregular, if not erratic.

In seeking an explanation for these results the possible influence of the adrenals was considered. A number of pertinent observations may be summarized. Thyroparathyroidectomized rats have a low resistance to cold and usually succumb after 1 to 6 days exposure to a temperature of 3-5°C. Adrenalectomized-thyroparathyroidectomized rats are even more sensitive to cold, death occurring usually after a few hours of exposure. Adrenalectomized rats are more sensitive to thyroxine than normal rats, both as regards the survival and the metabolic response. The fourth point needs more elaboration. In our rat colony adrenal insufficiency was produced somewhat more consistently by Schultzer's combined operation (14) in which the upper halves of the renal capsules are removed in addition to the adrenals. Animals thus operated are

extremely sensitive to cold, becoming moribund or succumbing within a few hours. This may occur not only several days after the operation, but long after (119 days in 2 cases) in the few animals which may survive (15). Rats which had become moribund on exposure to cold and were resuscitated often lived for many days after in a state of chronic adrenal insufficiency.

The difficulty of obtaining significant metabolism data in such animals is obvious. If the rat remains alive for 6 to 8 days, or longer, the presumption is that it is not suffering from adrenal insufficiency. On the other hand, if the deficiency has been produced, the rat does not survive long enough to obtain representative specimens of urine. Because of these circumstances we have succeeded only twice in securing data which we believe to be of value.

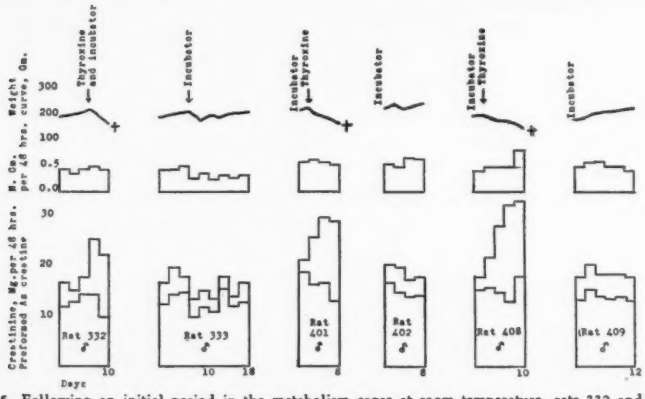


Fig. 5. Following an initial period in the metabolism cages at room temperature, rats 332 and 333 were transferred to a thermal environment of 33-34°C. Rat 332 received thyroxine, 2 mg. daily. Note depression of metabolism in rat 333 and relatively moderate effect produced by thyroxine in rat 332. Rats 401 (thyroxine-treated, 1 mg. daily) and 402 (control) were maintained at a temperature of 31-32°C. Rats 408 (thyroxine-treated, 1 mg. daily) and 409 (control) were kept at a temperature of 28-29°C.

The results of one of the successful experiments (Ad-9) are charted in figure 4 and show that the creatine-creatinine and nitrogen response is not abolished and is perhaps even somewhat exaggerated in the adrenalectomized rat.

On the basis of so few observations it is impossible to do more than speculate on the possibility that the lessened response on a second or subsequent exposure to cold may represent in the normal rat an antagonistic effect of the adrenals, stimulated to increased activity as the result of the first exposure; in short the inference is that the adrenals and thyroid may be interrelated in the regulation of creatine metabolism as they are in the regulation of respiratory metabolism (16, 17). Indeed our observations may not be unrelated to the recently reported demonstration by Koelsche and Kendall (18) of the antagonism of the adrenal cortical hormone to thyroxine in the maintenance of nitrogen balance in the dog.

Constancy of the metabolic response to cold and its modification or absence in the thyroparathyroidectomized rat. The characteristic increase in the excretion of nitrogen and creatine may be demonstrable during the first 48-hour period of exposure to cold, but usually becomes more definite during the second 48-hour period. Often metabolism is at first somewhat depressed, rather

than elevated, and occasionally the response is delayed, occurring as late as the 6th day (for example, rat 190, fig. 4). Nevertheless a clear-cut response is obtained almost invariably, a negative result having occurred only once in a series of 26 metabolism studies.

That the augmented creatine metabolism depends on the presence of the thyroid seems probable from the fact that it does not occur in thyroparathyroidectomized rats. In such animals the levels of nitrogen and creatine metabolism are subnormal. When exposed to cold, the nitrogen output is somewhat increased, but with rare exceptions (rat 154, for example) the total creatinine excretion is not altered significantly, although there may be a moderate increase of creatine at the expense of creatinine. Thyroid-deficient rats have a low resistance to cold and become moribund or die after several days' exposure to a temperature of 3-5°C. Rats found cold and comatose and on the verge of death have been often revived on transferring to a warm room. Thus, rat X-7 (fig. 4) tested 11 days after the operation became moribund on the 3d day. It was resuscitated and again tested 6 months later. A negative metabolism response (as regards total creatinine) was again obtained and the animal was found dead on the 3d day of exposure.

Thyroparathyroidectomized rats receiving small amounts of thyroid or thyroxine withstand exposure to cold as well as normal rats.

In connection with other work requiring a large number of hypothyroid rats, resistance to cold and the response in creatine metabolism, supplemented more recently by estimations of the guanidine acetic acid excretion, have been successfully employed as criteria in testing thyroid deficiency.

Metabolism at high temperatures. Exposure to very high temperatures is associated with degenerative changes in the thyroid both in normal and thyroxine-treated rats (1). Attempts to study metabolism above 34°C. were unsuccessful, partly because of the very low tolerance of rats to thyroid substance at such temperatures. Accordingly the present report is limited to several typical experiments at temperatures varying between 28 and 34°C. The results, represented in figure 5, may be briefly summarized as follows. A high thermal environment has a depressing effect on nitrogen as well as creatine metabolism. The administration of thyroxine (or desiccated thyroid) is followed by increased nitrogen and creatine excretion, the effect being relatively small at very high temperatures (33-34°C.) and becoming more marked as ordinary temperatures are approached.

SUMMARY

The normal rat exposed to cold shows a characteristic metabolic response, usually within 48-96 hours. This includes a rise in the excretion of nitrogen, creatine and guanidine acetic acid. The increases in endogenous (creatine-creatinine) and total protein metabolism seem to be related to thyroid activity, as they do not occur in the thyroidectomized rat. This and the low tolerance to cold may be employed as tests of thyroid deficiency in rats following extirpation of the gland.

Rats in which the level of endogenous metabolism is raised, either by the administration of thyroxine, or by exposure to cold, show fluctuations in total

creatinine excretion not observed normally. If the relative constancy of creatine metabolism normally is considered an example of physiological homeostasis, the variability under the conditions stated may be taken to represent an unsteady state of endogenous metabolism,—in short a condition of disturbed homeostasis.

In long-period metabolism studies an attempt was made to correlate the loss of creatine in the urine with the reserves in the tissues in rats with hyperthyroidism, induced either by the administration of thyroxine, or exposure to cold.

The irregularity of the responses observed in rats subjected alternately to low-temperature and normal environments and other data suggest an adrenal-thyroid interrelationship in the regulation of nitrogen and creatine metabolism.

The depression of nitrogen and creatine metabolism at high temperatures (33-34°C.) is only moderately augmented by the administration of thyroxine.

REFERENCES

1. Bodansky, M., J. F. Pilcher and V. B. Duff: J. Exper. Med. **63:** 523. 1936.
2. Kenyon, A. T.: Am. J. Path. **9:** 947. 1933.
3. Draize, J. H.: J. Pharmacol. & Exper. Therap. **39:** 259. 1930.
4. Draize, J. H. and A. L. Tatum: J. Pharmacol. & Exper. Therap. **42:** 262. 1931. Arch. internat. de pharmacodyn. et de thérap. **43:** 237. 1932.
5. Donaldson, H. H.: The Rat, Memoirs of the Wistar Institute of Anatomy and Biology, 2d edition, Philadelphia, 1924.
6. Smith, F. M. and E. M. MacKay: J. Exper. Med. **55:** 903. 1932.
7. MacKay, E. M. and L. L. MacKay: J. Nutrition **4:** 33. 1931.
8. Bodansky, M.: J. Biol. Chem. **112:** 615. 1936. **115:** in press. 1936.
9. Cannon, W. B.: Physiol. Rev. **9:** 399. 1929.
10. (a) Hunter, A.: Creatine and creatinine. Monographs on Biochemistry, London and New York, Pp. 223-5, 1928.
    (b) Bodansky, M.: J. Biol. Chem. **112:** 615. 1936.
11. Weber, C. J.: Personal communication; J. Biol. Chem. (Proc. Am. Soc. Biol. Chem.) **109:** xcvi. 1935.
12. Sakaguchi, S.: J. Biochem. **5:** 25. 1925.
13. Pugsley, L. I., E. M. Anderson and J. B. Collip: Biochem. J. **28:** 1135. 1934.
14. Schultzer, P.: J. Physiol. **84:** 70. 1935.
15. Bodansky, M., C. M. Agress, K. R. Campbell and C. L. Herrmann: Endocrinology. **20:** 684. 1936.
16. Marine, D. and E. J. Baumann: Am. J. Physiol. **57:** 135. 1921.
17. Davis, J. and A. B. Hastings: Am. J. Physiol. **105:** 110. 1933.
18. Koelsche, G. A. and E. C. Kendall: Am. J. Physiol. **113:** 335. 1935.

THE SIGNIFICANCE OF ELECTRICAL IMPEDANCE MEASUREMENTS ON THE HUMAN BODY

J. W. HORTON AND SAUL HERTZ

From the Department of Electrical Engineering, Massachusetts Institute of Technology and the Department of Medicine, Harvard Medical School and Massachusetts General Hospital

BOSTON, MASSACHUSETTS

In a recent paper, "The Impedance Angle and Thyroid Disease," Dr. M. A. B. Brazier (1) has severely criticized work along related lines which has been carried out jointly by the Department of Electrical Engineering of the Massachusetts Institute of Technology and the Metabolism Clinic of the Massachusetts General Hospital. This work has been reported in two earlier papers (2, 3). Brazier's comments are of a nature which seems likely to cause unwarranted confusion and misunderstanding regarding the true significance of our study. It appears desirable, therefore, to restate certain facts regarding this study, with particular emphasis on those points which have been brought into question. This is done in the hope of preserving that clarity of outlook without which the real value of any investigation must inevitably be obscured.

There are two major questions involved in the objections which Brazier has raised regarding the studies reported by us. One is concerned with the measuring technique; the other with the pathological significance of the quantities measured. The first involves facts. These are subject to exact verification and may be analyzed with mathematical rigor. Here both Brazier's results and ours may be appraised in terms of the numerical accuracy with which the quantities measured are determined. The second question involves judgment. Here it would seem that the more complete and reliable the data at our disposal the more dependable should be the conclusions. In this latter respect we have looked upon our work as a logical sequel to that reported some time ago by Brazier (4).

The Quantity Measured. In both Brazier's work and in our own the property measured is an electrical impedance. Electrical impedance is a physical property of matter and exists as such, quite independently of any method used for its evaluation. Brazier's statement that our technique measures a different property from hers is misleading.

Impedance is the property of an electrical circuit which determines the alternating current flowing in it under any given impressed alternating voltage. It is, by definition, the ratio of the applied voltage to the resulting current. In general, impedance represents the combined effects of two other properties, resistance and reactance. Like impedance, each of these simpler properties is defined as the ratio of a voltage to the accompanying current. They are distinguished by the fact that energy associated with current flowing in a resistance is entirely dissipated as heat,

whereas no energy loss results from the flow of current through a reactance. Resistance and reactance combine to give the magnitude of the resultant impedance in accordance with the following formula:

$$Z = \sqrt{R^2 + X^2}$$

where $Z =$ total impedance, $R =$ resistance component, $X =$ reactance component.

The relations between these quantities may be shown graphically by diagrams in which resistance values are plotted horizontally and reactance values are plotted vertically (see fig. 1). The resultant impedance is thus represented by a line of definite length, Z, making a definite angle, ϕ with the horizontal. This line is known as a vector and the angle as a vector angle. The magnitude of this vector angle is obviously fixed by the relative magnitudes of the resistive and reactive components. Its value is given by the expression

$$\tan \phi = \frac{X}{R}$$

Resistance, reactance and impedance magnitudes are each expressed in terms of the same electrical unit, the ohm. Impedances are added by adding their resistive and reactive components separately.

A point of great importance to the investigations in question appears here. Numerical values of the resistance, R, and of the reactance, X, depend upon the nature of the conducting material, upon its length and upon its area of cross-section. It is evident, then, given a homogeneous material, that a change in size or in shape of the sample measured will result in proportional changes in 3 of the above mentioned quantities, namely, R, X, and Z. It is also clear that these changes, being proportional, will not affect the vector angle, ϕ. For a homogeneous sample, therefore, this angle is a function of the nature of the material only and is independent of its size or shape. The appreciation, by Brazier, of the clinical convenience of this qualitative property of the vector angle must be considered a noteworthy contribution to the study of the pathological significance of electrical impedance.

Both in Brazier's work and in our own it has been found convenient to express numerical results in terms of the tangent of the vector angle rather than in terms of the angle itself. The use of this quantity is, of course, entirely permissible as the angle and its tangent are explicit functions of each other. Since our numerical values were those of the tangent we felt it desirable to so specify them and hence adopted the symbol which has for many years been used for this purpose by electrical engineers. The accepted symbol for this quantity is Q and the expressions Q, $\tan \phi$, and X/R are well understood to be equivalent. We feel strongly that the nomenclature suggested by Brazier, in which values of the tangent are referred to as angles, is without justification.

Brazier has suggested that we have called the result of our computation the 'internal impedance' with a new symbol, Q. This is not the case. The symbol Q is not new, does not stand for the impedance, and is not restricted to the internal tissues. It is well established in electrical technology as a convenient symbol to stand in the place of the expressions $\tan \phi$ or X/R. The 3 terms mean exactly the same thing.

The Selection of the Sample for Measurement. The essential difference between the technique used by Brazier and that developed by us is in the

selection of the portion of the body the impedance of which is to be determined. In her first paper (4) Brazier discussed the distinction between internal and surface tissues and reported on a series of measurements directed toward a determination of their respective contributions to the impedance of the total sample as measured by the immersion method. Brazier's results, together with our own initial investigations, suggested the desirability of a more direct evaluation of the impedances of these two constituents of the total sample. To this end we developed the 4-electrode method (2).

By placing 4 electrodes on the body and measuring the impedance between each of the 6 possible terminal pairs, data are obtained from which may be computed an electrical network exactly equivalent to the body. This equivalence is restricted to the frequency and amplitude of the current used in the original measurements. In general such an equivalent network would require 6 branches. In every measurement which we have made, however, we have found that the 6 observed impedances are not mutually independent, but that any 5 are sufficient to completely specify the network. The equivalent network, therefore, has 5 branches, (2, fig. 1, p. 561). The impedance of each branch may be exactly stated in terms of the impedances measured between the several terminal pairs. Should an actual network be set up having the arrangement shown and with the impedances computed by the formulae given (2, p. 561), it would be impossible, at the frequency and amplitude of current in question, to distinguish between the network and the body by any electrical measurements which might be made at the terminals. There exists such an equivalent network for each frequency at which measurements may be made. The constituent impedances evaluated by our 4-electrode method may be defined rigorously only in terms of these equivalent networks.

The data previously presented (2, fig. 2 and 3, p. 563) show that the several network branches have distinctive frequency-impedance characteristics. It is a resonable hypothesis to associate them with distinctive types of tissue. That our so-called surface sheath is, in fact, the skin is supported by the close correspondence between our results and those of bio-physicists who have made direct measurements on human skin and on frog skin (5). Further support for the supposition that branches S_{LT} and S_{RT} (2, fig. 1) are due to the surface sheath and branch B to the internal tissues, is found in the fact that the impedance of the immersed arm, computed on this assumption, agrees closely with values obtained by direct measurement (2).

As a result of the separate evaluation of the impedances of these two distinct types of branch it is now possible to study directly the contribution of each to any correlation between the electrical impedance of the body and its physiological condition. It certainly is not necessary to approach the conclusion that either the skin or the internal tissues may or may not be involved in such correlation through any process of deduction based on indirect evidence similar to that used by Brazier in her criticism of our work. Accurate numerical values may be established for each branch; these may be examined as such in conjunction with clinical classifications.

Reliability of Measurements. Brazier has referred to our use of a potentiometer as an essential difference between her technique and ours. It should be unnecessary to point out that the measuring instrument never alters a fact; it merely limits the accuracy with which the fact may be known. In this connection it seems in order to examine the relative accuracy of our measurements

and of those which Brazier has used in her comparative study.

In our work no measurement is regarded as acceptable unless the reactance value is believed to be good to at least 2 per cent. By the conditions required for balance, resistance values, although about 10 times as great as the associated reactances, are known to the same numerical accuracy. They have, then, one tenth the percentage error. The accuracy with which Q is known is thus determined almost wholly by the error in the reactance component and is, in consequence, likewise good to 2 per cent.

Such accuracy is necessary in studying certain interesting changes in impedance with fatigue, with position of the body, with portion of the body

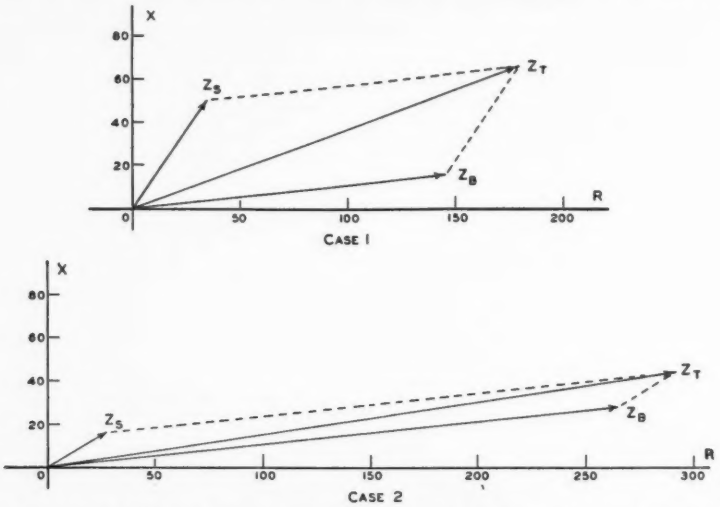


Fig. 1. Vector diagrams of the impedances of the constituent and total samples taken with band electrodes on the upper arms (case 1) and by the immersion method (case 2). Scale units are ohms. Vector angle is measured from R-axis. Significance of subscripts and numerical values are given in table 1.

measured, and with similar variables. To obtain this accuracy it is imperative that the body be reclining and completely at rest. Under these conditions the accuracy with which impedance measurements may be made is limited by variations in impedance accompanying respiration and pulsations in blood flow. These variations restrict the accuracy of measurement, with our present apparatus, to about 0.05 ohm.

In a previous paper (2, table 1) are shown the formulae by which the several constituent impedances of the human body may be computed in terms of the impedances measured between each of the terminal pairs of our 4-electrode arrangement. For the reason pointed out in the preceding section there are 2 formulae for each quantity. In other words, each quantity may be evaluated by either of two sets of data taken from the 6 observed values. By means of the comparisons thus afforded it is possible to obtain a numerical estimate of the accuracy of the data presented by Brazier in her recent paper (1). Having computed from this data the impedances of each of the 3 branches, S_{LT}, S_{RT} and B, for each of the 12 subjects, it appears that, on the average, resistance values do not agree within 2 ohms and

reactance values do not agree within 1 ohm. In some cases the agreement is perfect; in others the discrepancies are so great that computed values of Q for the internal tissues, which should be the same, differ by 10 per cent. It is our feeling that no significance can be attached to data in which the maximum error is as great as one-fifth this amount.

Results of Separate Measurements of Branch Impedances. To aid in a clear understanding of the relations between the several impedance quantities for the various body samples under consideration the vector diagrams of figure 1 have been prepared. The data are from the same subject as that for figure 4 (2). In the upper diagram are drawn to scale the vector quantities representing the impedances between band electrodes placed on the upper arms. The values for the lower diagram are those involved in the immersion method. To facilitate analysis of these impedances the numerical values of the individual

TABLE 1. VALUES OF THE SEVERAL IMPEDANCE QUANTITIES FOR CONSTITUENT AND TOTAL SAMPLES TAKEN WITH BAND ELECTRODES ON THE UPPER ARMS AND BY THE IMMERSION METHOD. DIAGRAMMATIC REPRESENTATION IS GIVEN IN FIGURE 1.

	Sample	R	X	Z	Q
	Case 1				
B	Internal tissues between band electrodes on upper arms	145.7	16.1	146.5	0.110
S	Sum of external tissues under band electrodes	34.6	49.8	60.6	1.44
T	Total sample between band electrodes	180.3	65.9	191.8	0.365
	Case 2				
B	Internal tissues between elbows	265.3	28.7	266.8	0.108
S	Sum of immersed arms	27.0	16.0	31.4	0.592
T	Total sample taken by immersion method	292.3	44.7	295.6	0.153

quantities, R, X, Z and Q, for each sample, are given in table 1. Particular attention is called to the following points.

Although the internal tissues included in the two cases are for different portions of the body and the magnitudes of their impedances are markedly different, the tangents of their vector angles, Q_{B_1} and Q_{B_2}, differ by only 2 per cent. This illustrates our claim that, to a first approximation, the internal tissues are homogeneous with respect to the quantity Q. The argument in favor of Q as an indicator of the quality of the sample has already been presented. The validity of this argument rests upon the assumption that the sample is homogeneous. It is therefore enhanced when the sample is composed solely of internal tissues. It was found early in our work, as already reported, that similar homogeneity was not present in surface tissue.

The resistance of the total sample, in case 1, is due largely to the resistance of the internal tissues. It is, therefore, greatly influenced by the location of the band electrodes. The reactance of the total sample is due largely to the reactance of the surface tissues. It, then, is greatly influenced by the size of the band electrodes. The value of Q for the total sample, being the ratio of these quantities, is thus dependent upon both the size and the location of the electrodes. It does not measure an inherent property of the body.

It is evident from an examination of the values of the impedance quantities shown in the table that the only one which is the same in the two cases is the quantity Q for the internal tissues. It is also true that, of all the quantities listed for each case, this one only is almost wholly independent of factors subject to the discretion of the observer and is determined solely by the properties of the tissues.

This exhibit demonstrates the interrelations between the several impedance quantities of both constituent and total samples for two different body connections. Brazier's statement that the quantities appearing in our method bear no relation whatever to those appearing in hers is obviously a denial of the laws of mathematics and of electrical technology. The relation is that of the parts to the whole.

The two cases illustrated above were selected because they are those for which Brazier claims significant relations between the impedance of the total sample and thyroid condition. She also claims that the impedance of the internal tissues shows no such relation. These conclusions are not consistent when viewed in the light of established facts. The internal tissues have been shown to contribute a major portion of the impedance of each of the total samples. The contribution of the surface tissues has been shown to be dependent upon the details of the electrical connections. The two contributions are certainly independent of each other, as the two types of tissue may be combined in any arbitrary manner. It must follow, therefore, if the impedance of the internal tissues bears no relation to a given condition, that the impedance of any sample of which these tissues are a major constituent must also be unrelated to that condition.

INTERPRETATION OF RESULTS

In this section it is particularly important to distinguish clearly between verifiable facts, statistical evidence, and conclusions based on statistical evidence. The statistical evidence underlying our conclusions as to the relation between electrical impedance and thyroid condition may be summarized as follows:

A) The quantity Q shows a tendency to have lower values for hyperthyroids and higher values for hypothyroids than for normal subjects of the same sex. This is reported by several investigators who have used the Brazier technique. We have shown that it is particularly true when the internal tissues are measured alone. In addition to the data which have already been published on this point may be shown the data plotted in figure 2.

B) The quantity Q for hyperthyroids shows no tendency to approach the normal range with iodine medication. This, again, has been established by a number of observers during studies based on the Brazier technique. As shown before (3, fig. 5), it is also found to be the case for the internal tissues alone.

C) The quantity Q for hypothyroids shows some tendency to vary toward the normal range as a result of treatment with thyroxin. This is clearly shown, for the internal tissues, in the previous paper (3, figure 4, chart E).

D) The quantity Q for the internal tissues of a considerable number of

miscellaneous non-thyroid hospital cases has been found by us to have values outside, and particularly below, the normal range. This is well illustrated in figure 2. There is little evidence regarding similar cases measured by the Brazier method, except that recently reported by Robertson and Wilson (6). No obvious correlation was found for the commoner disorders present in medical and surgical wards. A single case of Addison's disease was examined and found to be below the normal range. An important point in connection with evidence pertaining to a situation of this character should not be overlooked;

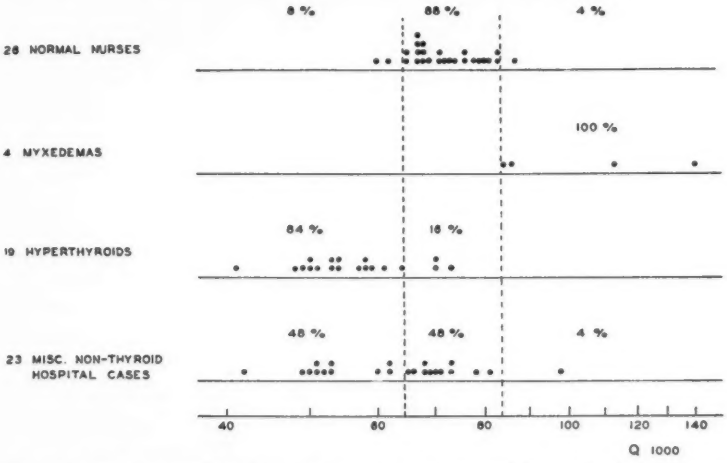


Fig. 2. Values of the quantity Q for the internal tissues, measured between band electrodes on the upper arms, at 10 kilocycles, for 72 women. Percentage distributions in three arbitrarily assigned ranges are shown.

more data are required to indicate that it does not exist than is sufficient to prove that it does.

E) Values of the quantity Q for the internal tissues are not indicative of the B.M.R. (3, fig. 6, 7). It is also true for non-thyroid patients.

F) There is some slight evidence that the value of the quantity Q for the internal tissues, in hyperthyroids, rises following thyroidectomy. This has been found in cases showing no change in B.M.R.

There appears to be general agreement regarding the first three of the above statements in so far as they apply to data taken by the immersion method. The only data other than our own on the internal tissues is that covering the 12 cases reported by Brazier (1). This appears not to confirm our findings. We believe, however, that the number of cases covered by our investigations, together with the accuracy which we know to hold for our measurements, entitles our data to consideration. If the validity of our data is admitted it will be found to support our conclusion that the statistical evidence as to the relations between impedance and thyroid condition found in data taken by the Brazier method appears even more clearly in data taken on the internal tissues alone.

Our conclusions, reached after a careful study of the evidence summarized

above, are as follows. *A*) Determinations of the quantity Q cannot be used in place of determinations of B.M.R. because of lack of concurrence between them. *B*) The quantity Q is not a specific indicator for thyroid condition because other pathological causes have been found which give the same deviations from normal.

Brazier's argument in favor of using impedance data in place of the B.M.R. is obviously based on her belief that it yields more pertinent information regarding thyroid condition. Assuming this to be true it must be conceded that it does not yield the same information. In consequence we feel that, while one measurement may supplement the other, it cannot replace it.

The second point where Brazier's conclusions and ours differ involves the clinical utility which may be ascribed to impedance data. Although the existence of a relation between the quantity Q and thyroid activity has been clearly demonstrated we are not yet willing to recommend the introduction of impedance measurements into general diagnostic practice.

An examination of Brazier's criticism of our work discloses that it is based, not on any fallacy in our fundamental technique, nor on any error in our measurements, but on our conclusions. The obvious primary basis for her objections is found in the following statements (1). "With such widely differing techniques there is little reason to expect any close concordance in the results obtained, nor have Horton, Van Ravenswaay, Hertz and Thorn (10) demonstrated any such concordance, yet they assume that their results may be used to dispute conclusions arrived at by other workers who have been concerned with the impedance angle of the body measured by the Brazier technique." And again: "Since in spite of their obvious recognition of the wide difference between the methods they still make the tacit assumption that their failure to obtain significant results entitles them to dispute the properties of the impedance angle as established by workers using the Brazier technique."

We believe that concordance between the results has been fully demonstrated, both factually and statistically. Our conclusions as to the clinical value of the Brazier method are based on data taken by that method. We believe that significant results have been obtained by measurements on internal tissues alone. We do not dispute the properties of the impedance angle, only the conclusions as to the present utility of these properties in indicating thyroid condition.

REFERENCES

1. Brazier, M. A. B.: Endocrinology **20:** 621. 1936.
2. Horton, J. W., and A. C. Van Ravenswaay: J. Franklin Institute **220:** 557. 1935.
3. Horton, J. W., A. C. Van Ravenswaay, S. Hertz, and G. W. Thorn: Endocrinology **20:** 72. 1936.
4. Brazier, M. A. B.: J. Instit. Elect. Engineering: **73:** 204. 1933.
5. Cole, K. S.: Cold Spring Harbor Symposia **1:** 112. 1933.
6. Robertson, J. D., and A. T. Wilson: J. Physiol. **85:** 23. 1935.

CASE REPORTS

THYROID DYSFUNCTION IN HEMOCHROMATOSIS

M. NORMAN ORGEL AND DAVID BARR
From the Department of Medicine of Washington University and the Barnes Hospital
ST. LOUIS, MISSOURI

In the peculiar condition of hemochromatosis the deposit of iron containing pigment is widespread and is known to involve many structures including, among others, several of the glands of internal secretion. Altho its effect on the anatomy and function of the liver and pancreas has been much emphasized, the results of its presence in other glandular structures has been less studied. Our interest in the subject was stimulated by observation on the following case in which, in addition to involvement of the pancreas and the liver, there were many evidences of disturbance in the function of the thyroid gland.

The patient was a 44 year old white male, a private patient of Dr. Oliver Campbell, who first entered Barnes Hospital on May 15, 1933. He had been a traveling salesman up to a year before admission when, because of his complaints, he changed to an office position. The family history was irrelevant. The past history was negative except for a Neisserian infection 10 years before. For the past year he had been nervous, easily irritated, and upset. During this time he had noted a fine tremor of his fingers. About 2 weeks before admission he had noticed that, at the end of the day, his ankles would swell. During the past year he had lost some 20 lb. He had gone to his physician who told him that his pulse was rapid. On admission to the hospital, examination showed a well-nourished white man weighing 151 lb. and looking his age. His skin was warm and moist and his palms were damp. No unusual pigmentation was noted. The palpebral fissures were widened and there was a lid-lag. The pre-tracheal region was full; the thyroid was soft, easily palpable but was recorded as not enlarged. The heart was slightly enlarged to the right. Pulse was 108; blood pressure (brachial artery) 166/72. The liver edge was palpable 2 finger-breadths below the costal margin; the edge was hard and irregular but not tender. There was a fine tremor of the extended fingers. The blood count and the differential smear were essentially normal except for a 3 per cent eosinophilia. The Kahn was negative; the N.P.N. was 33 mg. per cent. The urine showed a 3+ sugar. A sugar tolerance test (true sugar values) showed:

Fasting blood sugar	113 mg. %	urine negative
Half hour after meal	287 mg. %	urine negative
One hour after meal	298 mg. %	urine 4+ sugar
Two hours after meal	347 mg. %	urine 4+ sugar
Three hours after meal	261 mg. %	urine 4+ sugar

His basal metabolic rate on May 16 was +16 per cent. The electrocardiogram showed nothing abnormal. He was put on a diet of protein 70, fat 150 and carbo-

hydrate 150 gm., without insulin and his urine remained sugar free. He was instructed as to the measurement of his diet and discharged on May 25, 1933, with a diagnosis of diabetes mellitus and questionable hyperthyroidism. At this time he was put on Lugol's solution.

He was first seen in consultation on July 10, 1933. At that time there was a moderate exophthalmos and a lid-lag. The thyroid was slightly enlarged but there was no bruit. There was a fine tremor of the outstretched fingers. The pulse was rapid and the blood pressure was 110/70. The liver edge was felt 3 finger-breadths below the costal margin and was very hard and thick. The spleen projected 2 finger-breadths below the costal margin and could be percussed back to the posterior axillary line. His physician had been impressed by the increasing brownness of his skin and the patient's sister had also noted this, although it had escaped the attention of the patient himself. Because of these findings, the diagnosis of hyperthyroidism was confirmed and a tentative diagnosis of hemochromatosis was made. The speculation arose as to whether the diabetes was primary, or was associated either with the hyperthyroidism or a possible hemochromatosis. Another B.M.R. was obtained on July 12th, and this was +12 per cent. He was taken off all iodine and 3 weeks later his basal rate was +37 per cent. In the interval he had lost about 8 lb. His pulse had become more rapid but he showed no evidence of decompensation. His course at this time suggested that this was a case of hyperthyroidism with diabetes as a secondary manifestation. He was instructed to rest at home without any iodine for 2 months and then to have a thyroidectomy.

He re-entered Barnes Hospital on Sept. 11, 1933. He had noted no change from his previous condition except that he had lost 40 lb. since his first admission, that now swelling of his ankles was more frequent, and that exertion was accompanied by dyspnea. He had remained on his diet and there had been no glycosuria. At this time drowsiness and apathy became marked and consequently a history was difficult to obtain. Examination showed the patient to be malnourished with a greyish-brown pigmentation of the skin of the forearms, the postero-inferior portion of the neck, and the lower portion of the legs. A biopsy of a deeply pigmented area of skin failed to reveal any iron containing pigment. At this time no exophthalmos or lid-lag was noted. There was a bruit over the thyroid isthmus. The pulse was full and bounding and the blood pressure was 120/70. There was fine tremor of the fingers and tongue. The liver and spleen presented the same characteristics as on the previous examination. The genitalia were normal. The B.M.R. on Sept. 12th was +19 per cent. Although the picture of thyrotoxicosis was not so marked as it had been before, it was still thought advisable to perform a thyroidectomy because of the increasing severity of the diabetes.

The patient was given Lugol's solution from Sept. 13th to Oct. 14th with a marked drop in the B.M.R. To prepare the patient for thyroidectomy, he was put on a diet of protein 60, fat 150, and carbohydrate 300 gm., which he was able to take without glycosuria and with a fasting blood sugar of about 110 mg. per cent. On Sept. 16th the patient had 2 chills with a spike of fever going to 40.6C. Physical examination showed no change over the previous examination except for absence of abdominal reflexes and the presence of bilateral Gordon, Kernig and Babinski reflexes. To rule out encephalitis, a lumbar puncture was made but this showed nothing abnormal. The patient had no further fever until just before death. His stupor gradually increased and he was obviously losing ground rapidly. Because of this a thyroidectomy was definitely out of the question. By this time his B.M.R. was below zero per cent but, when Lugol's solution was discontinued, it still contained to fall (fig. 1). On Oct. 14th when his B.M.R. was definitely below zero he began to run a

consistent glycosuria and a high blood sugar which persisted after decreasing the carbohydrate intake to 250 gm. At first he could be controlled with 10 to 20 U. of insulin daily but almost day by day his insulin requirement rose till on Nov. 20th he was receiving 80 U. daily. This rapid reduction in glucose tolerance, in spite of the marked drop in the basal rate indicated that there was no controlling relationship between the glycosuria and the hyperthyroidism. On Oct. 25th it was noted that the apical heart rate was very rapid. An electrocardiogram showed an ectopic auricular tachycardia with occasional short runs of total irregularity. The rate was 180. This persisted till death. He became more and more stuporous, finally developed a bronchopneumonia and died on Nov. 22d, 1933.

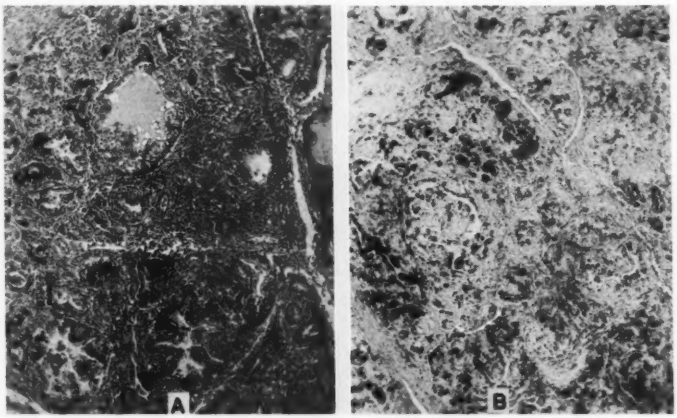


Fig. 2. The thyroid at post-mortem examination: *A*, hematoxylin and eosin stain, showing extensive hyperplasia and fibrosis; *B*, iron stain showing distribution of pigment.

Post-mortem examination was made by Dr. Russell Blattner 1½ hours after death. The heart was slightly enlarged, weighing 370 gm. There was a bronchopneumonia. The spleen was enlarged and weighed 500 gm. The Malpighian bodies did not stand out clearly and the pulp was very hemorrhagic in appearance. The pancreas, liver, and thyroid were all a dark brown or chocolate color. The pancreas seemed to contain more than the normal amount of fat. The liver was large and weighed 1550 gm. It showed a typical hobnail cirrhosis. The thyroid was of normal size and firm in consistency but the deep brown pigmentation was striking. The brain was extremely edematous. A small cyst was present in the anterior lobe of the pituitary. The choroid plexus was stained a deep brown.

Microscopic Examination

Heart. Practically every muscle bundle contained iron pigment, which tended to be arranged at the poles of the nuclei and was present in both the auricle and ventricle. There was a small amount of pigment in the connective tissue, especially just below the endocardial surface.

Lungs. The alveoli were air-filled, the septal walls thin and delicate. There were occasional collections of polymorphonuclear cells and bacteria. Iron stains showed practically no iron in the alveolar walls. Collections of carbon pigment were numerous.

Gastro-intestinal tract. The stomach and intestinal tract showed no lesions.

Lymph node. A lymph node from the region of the pancreas was heavily laden with iron pigment. Many active germinal centers were seen. Most of the pigment was found in the tissue between these centers.

Thyroid. There was a marked overgrowth of fibrous tissue throughout the gland and one received the impression that in many places the fibrous tissue had squeezed out the alveoli. There was an extreme degree of iron pigment deposition situated, for the most part, in the free portion of the secretory cells, but to some extent in the connective tissue. In a few places some iron granules were found in the colloid. About ⅓ of the alveoli were lined by cuboidal or low columnar cells and contained firm, deep-staining colloid. The remainder showed varying degrees of hyperplasia. In many places the alveoli contained little or no colloid, the alveolar cells were all cuboidal, were thrown up into folds, and presented the typical appearance of the hyperplasia of exophthalmic goitre (fig. 2, *A* and *B*). The degree of hyperactivity appeared to be roughly proportional to the amount of pigmentation present.

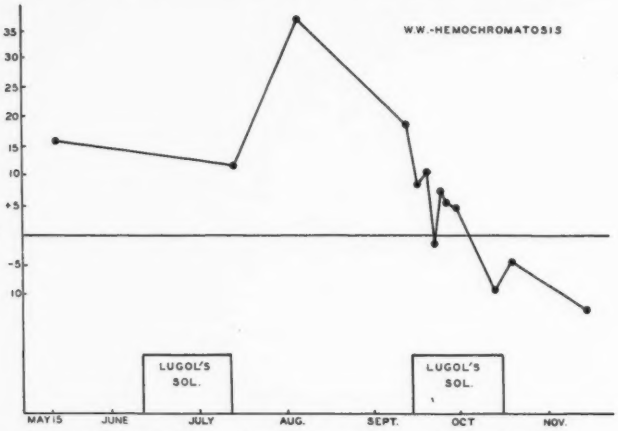


Fig. 1. Showing variations and gradual reduction in the basal metabolic rate.

Pituitary. In the anterior lobe there was a small cyst lined by columnar epithelium. The gland in general appeared normal. All cellular elements were present in approximately the usual amount. There were a few iron granules diffusely scattered in the cells of the anterior lobe, affecting about equally all the cell types. A few granules taking the iron stain were found in the posterior lobe.

Liver. The capsule was slightly thickened and was wavy in outline due to scarring. The liver architecture was distorted by firm bands of fibrous tissue which separated the tissue into lobules. The fibrous bands ran from portal area to portal area so that the bile duct and vessels were surrounded by fibrous tissue. The remaining liver tissue showed fatty infiltration. All over the organ clumps of brown pigment were apparent. It was most abundant in the liver cells but the epithelium of the bile ducts were also involved. Smaller amounts were seen in the fibrous tissue strands.

Pancreas. There was a moderately great increase in fibrous tissue throughout the gland. The islands of Langerhans appeared to be moderately decreased in number but many were increased in size. Deposition of iron pigment was marked throughout the gland, but was less prominent in the island tissue. There were masses of regenerating pancreatic alveoli containing a decreased amount of pigment. The duct epithelium contained a moderate amount of pigment near its free border.

Adrenals. The adrenal showed no changes except for moderate pigmentation almost entirely limited to the cells of the zona glomerulosa.

Kidneys. The capsule was not thickened. The glomeruli appeared normal and the capillary tufts were filled with blood. No pigment was seen in the glomeruli. The tubules showed no significant changes except for the deposition of pigment which seemed to be limited to the distal convoluted tubules, the ascending limb of Henle and some of the collecting tubules. The pigmentation was unusual in that only a small portion of the total number of tubules were affected.

Skin. The section stained with H. and E. did not reveal definite pigment. With the iron stain, however, the blue staining granules were readily seen. No pigment was found in the epidermis. A few clumps of granules were readily seen just below the epidermis, but most of the pigment was found deeper and about the glands.

DISCUSSION

The striking feature of this case was the hyperthyroidism which under observation became at first more severe, and then disappeared completely. This clinical picture, when considered with the finding of hyperplasia and fibrosis of the thyroid gland, leads to the suspicion that the deposition of iron in the thyroid may cause irritation and hyperplasia, and that, with continuance of the process, fibrosis and compression may produce decreased activity of the gland.

Of the 312 cases of hemochromatosis in the literature (1), there are 19 in which determinations of the B.M.R. have been made (1-14). The rates varied widely from —28 to +45 per cent but it is not possible from the data to judge at what stage in the disease the observations were made. In 3 the basal rates were determined more than once. In case 3 of Althausen and Kerr (2), and in the case of Labbé and his associates (9), there seemed to be a tendency to lessening of the thyrotoxicosis as the disease continued.

Author	*Date*	*Basal Metabolic Rate*
Althausen and Kerr (2) Case 3	Dec. 1	+19.6
	Dec. 2	+34.4
	Dec. 7	+19.5
	Dec. 27	+10.6
	Jan. 13	+ 7.5
	Jan. 28	+ 4.1
Labbé, Boulin, Azerad, and Uhry (9)	Dec. 22	+22.
	Dec. 27	+25.
	May 16	+ 9.
Cann (4)	Oct., 1930	− 2.
	May, 1932	+11.

Relevant to this discussion is the very interesting case which Berg reported in 1899 (15). His patient was a woman of 44 who 9 years previously had had an exophthalmic goitre with the usual signs of hyperthyroidism. She was treated by electrotherapy and hydrotherapy and gradually showed marked improvement with a gain in weight up to 6 months before Berg's observation when there were symptoms of diabetes, enlargement of the liver, and pigmentation, and when a diagnosis of hemochromatosis was made. At that time, although she showed only a slightly enlarged thyroid, the exophthalmos was still fairly marked. As the effectiveness of such treatment for hyperthyroidism

is not usually notable, it appears not unlikely that the changes in thyroid activity may have been due to the same factors that were responsible in our case.

If hyperthyroidism were common in hemochromatosis, one might expect to find evidence of hyperplasia of the thyroid post-mortem. Of the 45 cases we have been able to find in which the thyroid was examined microscopically, only 3 showed definite hyperplasia (2, 9, 16). In 2 of these the B.M.R. was determined. One (2, case 4) had a basal rate of +14 per cent 3 months before death. The other (9, 17) had a basal rate of +32 per cent and at autopsy the thyroid showed small vesicles with very little or no colloid but with flat epithelium.

In every case in which the pituitary has been described microscopically, there has been a deposition of iron pigment in the gland, frequently to a marked degree. In one case of Althausen and Kerr there was almost complete destruction of the anterior lobe. In view of this frequent pigmentation of the hypophysis, one might attempt to explain the changes in thyroid activity as secondary to changes in the thyrotropic activity of the pituitary. If, in our own case, the hypophysis had been responsible for the variations in thyroid activity, the anterior lobe must have gone through a phase of stimulation followed by inhibition due to damage to the gland. While it cannot be denied that the very small amount of pigment in the anterior pituitary might have caused functional change, the absence of histological alteration makes it improbable that this was a controlling factor.

The apathy and listlessness that this patient exhibited were in striking contrast to the hyperkinesis usually seen in thyrotoxic patients. This lethargy has been described by numerous observers. Sheldon believes it may be due to general depression of bodily functions because of the pigmentation. In view of the pigmentation of the zona glomerulosa of the adrenal gland in all cases in which the adrenals have been described and the similarity of the mental state to that seen in Addison's disease (18), some investigators believe that this manifestation is secondary to involvement of the adrenal cortex.

In this case and in other cases of hemachromatosis in the literature, it seems apparent that the thyroid gland was stimulated by the presence of pigment. It is known that the thyroid is one of the most labile structures of the body and that hyperplasia may be induced by a great variety of influences, such as infection, drugs, lack of iodine, etc. Among these many stimulating factors must be included the iron-containing pigment of hemochromatosis.

This consideration suggested the possibility that some cases of clinical hyperthyroidism might be dependent upon an unrecognized disturbance in pigment metabolism. We, therefore, examined the microscopic sections of the last 101 thyroidectomies done at Barnes Hospital. Of these, 20 showed significant accumulations of iron pigment. Seventeen of these 20 were cases of hyperthyroidism, 2 showed carcinoma of the thyroid, and 1 was a goitre associated with hypothyroidism. In no case was there any evidence of a diffuse deposition of iron which would lead us to suspect hemochromatosis. In all cases the pigmentation was limited to a few small areas of the section in which there was an increase in fibrous tissue. The pigment was almost entirely limited

to the interstitial tissue and only very rarely involved the secreting cells. The remainder of the section showed no evidence of iron. As the frequency of hemorrhage in hyperplastic thyroid glands is so well known, we believe that this deposition of iron is due to extravasation of blood which, when resultant fibrosis set in, was held in the fibrous tissue. The breakdown of the hemoglobin left the iron pigment.

SUMMARY

In hemochromatosis, the functional activity of the thyroid may depend on the response produced by the deposit of iron pigment. The case presented here and other cases in the literature suggest that at first the pigment increases the thyroid activity, but, as pigment deposition increases and fibrosis sets in, there is a progressive decrease in function.

Examination of 101 thyroid glands removed at operation presents no evidence to suggest that the deposit of iron pigment is a frequent cause of hyperthyroidism.

REFERENCES

1. Sheldon, J. H.: Hemochromatosis. Oxford Univ. Press, 1935.
2. Althausen, T. L. and W. J. Kerr: Endocrinology **11:** 377. 1927. **17:** 621. 1933.
3. Bufano, M.: Policlinicio (sez. med.) **40:** 273. 1933.
4. Cann, G. A.: U. S. Nav. M. Bull. **31:** 305. 1933.
5. Coro, A. J. and Zayas, C.: Ann. de vitas digests sangre y nutrición, **2:** 75. 1930. (Quoted by Sheldon).
6. Darnell, J. R.: Ann. Int. Med. **8:** 1121. 1935.
7. Dumphy, J. J.: Boston M. & S. J. **190:** 441. 1924.
8. de Gennes, L., J. Delarue and R. de Vericourt: Bull. et mém. Soc. méd. d. hôp. de Paris 1088. 1935.
9. Labbe, M., R. Boulin, B. Azerad and P. Uhry: Bull. et mém. Soc. méd. d. hôp. de Paris **47:** 542. 1931.
10. McClure, C. W.: Arch. Int. Med. **22:** 610. 1918.
11. Maddox, K. and E. B. Durie: M. J. Australia **1:** 463. 1934.
12. Marsh, P. L.: Endocrinology **8:** 795. 1924.
13. Sempau, S. A.: Sobre la Diabetes Bronceada. Trabajos del Servicio de Patologia Médica del Dr. Marañon. Año. 3. Madrid, Ruiz, 1929. (Quoted by Sheldon).
14. Wood, F. C. and T. Fitz-Hugh: Arch. Int. Med. **44:** 882. 1929.
15. Berg, H. W.: Medical Record **56:** 881. 1899.
16. Potter, N. B. and L. S. Milne: Am. J. M. Sc. **143:** 46. 1912.
17. Labbé, M., R. Boulin and M. Petresco: Bull. et mém. Soc. méd. d. hôp. de Paris **48:** 440. 1932.
18. Telling, W. H. M.: Brit. M. J. **2:** 784. 1921.

FUGITIVE ACROMEGALY. ACROMEGALY FOLLOWED BY PITUITARY CACHEXIA

TREATMENT WITH AN ALKALINE EXTRACT OF THE ANTERIOR PITUITARY

E. KOST SHELTON, LYMAN A. CAVANAUGH AND PAUL R. PATEK

From the Departments of Medicine and Anatomy, University of Southern California

LOS ANGELES, CALIFORNIA

Clinical studies of pituitary cachexia (Simmonds' disease) (1) are fairly common. Calder (2) reviewed the literature up to 1932 and cited 70 cases. Since this time several new observations have been recorded. In no instance was reference made to a preceding acromegaly. Pituitary cachexia in its severest form denotes failure of the entire hypophyseal mechanism or at least complete failure of the anterior lobe. In 1928 Bailey and Cushing (3) described a syndrome termed 'fugitive acromegaly' in which the early evidences of acromegaly were replaced by a state of pituitary embarrassment. The terminal phenomenon, namely, cachexia, weakness, increased carbohydrate tolerance, etc., may well have been due to a failure of the acidophilic elements alone. Controlled clinical observations of such a selective pituitary deficiency are comparatively rare.

The purpose of this paper is to present a diagnostic and therapeutic study of what the authors believe to be a case of 'fugitive acromegaly'. In this individual an opportunity was presented to survey a more or less selective deficiency producing a group of physiological phenomena which could be ascribed to aberrant secretion of the acidophilic elements alone. In addition it has been possible to evaluate the effects of certain types of therapy under controlled conditions. For these reasons a detailed report with discussions may prove of value.

The patient had completed 2 years of medical study prior to the onset of his disorder. His coöperation throughout the period of observation (23 months) was of the highest order. In so far as possible standardized preparations were used throughout the experiment. An attempt was made to measure the effect of contaminating fractions during the period of administration and to evaluate the effect of foreign substances by periodically discontinuing or altering the regimen.

CASE REPORT

P.R.P., a single, white male, aged 25 years, consulted us in July, 1933, complaining of anorexia, loss of weight and asthenia. A history of early otitis media, appendectomy at the age of 7 and influenza at 13, all without sequelae, was obtained. Otherwise the patient had enjoyed robust health until March, 1931.

Family History. The father, aged 61 years, had suffered from pulmonary tuberculosis and later toxic goiter followed by thyroidectomy. The mother, aged 56 years, aside from migrainous attacks, was in good health.

Onset and Progress. The onset occurred acutely on March 7, 1931 without antecedent history of illness or trauma. It was initiated by a severe pulsating headache followed by blurring of vision and diplopia. A consulting neurologist recorded an ocular neuritis, stiffness of the neck and loss of deep reflexes. The diagnosis of "some form of meningitis" was made. A mild fever, ranging from 101 to 102°F. ensued and lasted for 8 days, after which the headache disappeared and the deep reflexes returned. The following 4 months were spent in comparative well-being. Polydypsia and polyuria then appeared and lasted for 1 month. Subsequently, anorexia, weakness and weight loss appeared, all of which have persisted throughout the course of the illness. Five months after the onset of polydypsia and polyuria, he weighed 140 pounds, a loss of 47 pounds. Roentgenograms of the skull at this time showed a large sella and large frontal sinuses. The calvarium was thickened with irregular patches of calcification. Roentgenograms of the chest revealed no pulmonary disease. Basal metabolic rate estimations ranged from —35 to —40 per cent. On the basis of this depression and because of his complaints of lethargy and sensitivity to cold, he was given desiccated thyroid (U.S.P.) 3 to 6 grains daily. The onset of cardiac palpitation and nervousness necessitated withdrawal of the medicament after a few weeks. The following year (1932) smaller doses of thyroid were prescribed. Thyrotoxic symptoms again ensued and there was no relief from complaints. While the hands were large and spade-like, there was no progressive enlargement of either hands or feet. No changes were discovered in the eye-grounds or visual fields and repeated roentgen studies revealed no progress in the enlargement of the sella. By this time, however, several consultants suspected acromegaly and pituitary irradiation was considered. Because of the conflicting findings, the patient consulted us in July, 1933.

Present Complaints. He weighed 59.9 kg. (129.5 lb.), having lost a total of 27 kg. (59.5 lb.). This weight loss had been gradual and had been accompanied by progressive asthenia and somnolence. Libido and potentia remained unimpaired. While he was not totally incapacitated, the gradually diminished energy required a curtailment of active duties. The mentality remained alert and of a high calibre. No changes in character, emotionality or disposition were noted.

Physical Examination revealed an emaciated individual of pale, pasty complexion with prominent facial bones, particularly the frontals and the zygomatic processes. The height was 174.7 cm. (68.7 in.) and weight was 60 kg. (129.5 lb.). The optimal weight estimation according to the method of Willoughby (4) was 73.2 kg. (161.0 lb.). There was no gross disproportion in the skeletal measurements. The skin was dry and cold but not thickened. No abnormal skin pigmentation or hair distribution were noted. The hands were large and spade-like. The feet did not appear enlarged (shoe size 8½). The palpebral fissures were widened. The eye-grounds and visual fields were normal. The thyroid was palpable but not enlarged. There was no malocclusion or widening of the interdental spaces. The cardiac borders were within normal limits, the sounds were of good quality and no murmurs could be elicited before or after exercise. The rhythm was regular and the rate 70. The blood pressure in a sitting posture was 108/70 mm. Hg. in both arms; upon reclining, 116/80.[1] There were no abnormal findings in the chest or abdomen. The patient appeared greatly fatigued during the examination but was co-

[1] A fall in blood pressure in the upright position has been observed in hypopituitary and in hypoadrenal states and has been designated as the Schellong-Strisower phenomenon.

operative. Speech was slow, the voice monotonous and low in pitch. The facies appeared somewhat mask-like and the expression changed slowly. The cranial nerves were entirely normal. There were no disturbances of gait, associated movements or coördination. Superficial and deep sensations were intact. Reflexes were sluggish but otherwise normal. Muscle tonus was poor. The strength of grip as measured by a dynamometer was 120 in the right hand as compared with 100 in the left. No trophic or vasomoter disturbances were discovered.

Roentgen studies of the right hand (fig. 1) showed a tufting of the distal phalanges and hooking of the thumb with thickening and other bony changes characteristic of early acromegaly. Similar changes, but less prominent were found in the right foot. Studies of the spine disclosed no bony disorder. Stereoscopic studies of the skull (fig. 2) revealed the antero-posterior diameter of the sella as measuring

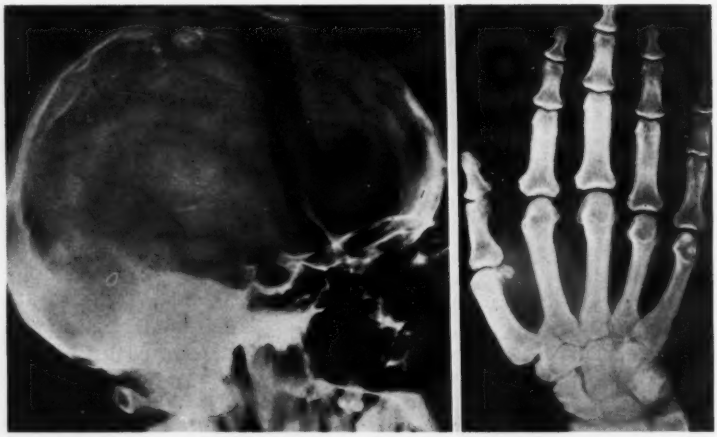


Fig. 1. (Right) Roentgenogram of patient's hand showing heavy bony structure, tufting of distal phalanges and hooking of thumb. Roentgenogram of patient's skull (Left) showing enlarged sella and calcified area. This calcification when examined stereoscopically appeared to be within the sella.

1.6 cm.; the floor of the skull through the sella measured 15.5 cm. The anterior and posterior clinoid processes were unusually thick. A small spur, several millimeters in length, upon the posterior clinoids extended posteriorly from a point mid-way between the tips of the clinoids and the base of the dorsum sellae. The floor of the sella was smooth with no evidence of erosion or of pressure displacement. A faint circular opacity approximately 5 mm. in diameter was noted within the sella. The bony calvarium showed excessively large frontal sinuses. A calcified pineal shadow was present but not displaced. The conformity of the frontal region, the development of the sinuses and the prominence of the jaw suggested acromegaly.

Laboratory Findings, on admission, were as follows. The red blood cell count was 4,500,000; white cells, 8,330; polymorphonuclears 47 per cent; lymphocytes 42 per cent; mononuclears, 5 per cent; transitionals, 2 per cent; eosinophiles, 3 per cent; basophiles, 1 per cent. The blood Wassermann reaction was negative. The urine findings were normal. A water retention test (Kamm) was made. Administration of a liter of water orally led to an output of 140 cc. in 4 hours. The output was the same in a similar period of time when 0.3 cc. obstetrical pituitrin was administered concomitantly. A glucose tolerance test gave the following capillary blood sugar values: fasting, 100 mg. per 100 cc.; ½ hr., 115 mg.; 1 hr., 90 mg.; 2 hr., 90 mg.

3 hr., 80 mg. No sugar appeared in the urine. Basal metabolic rate estimations, on different days, averaged —27 per cent.

In view of these findings it was felt that the patient suffered from a transitional form of pituitary disorder in which a primary hyperactive state had been replaced by a modified form of pituitary cachexia. A therapeutic test with alkaline extracts of the anterior pituitary seemed advisable.[2] Two cc. was administered intramuscularly daily, at intervals, over a period of 20 months. The effect of these extracts on weight, basal metabolic rate, blood pressure and muscular strength are shown in chart 1. The study has been interspersed with control periods without medication, others with thyroid therapy and still others with large doses of a glycerin extract of adrenal cortex by mouth. It will be seen that the patient gained weight rapidly during the first 6 months of pituitary therapy and that the administration of thyroid for 6 weeks led quickly to weight loss. Resumption of the pituitary fractions led again to weight gain which was subsequently followed by weight loss as soon as the treatment was withdrawn. This apparently was a therapeutic confirmation of the diagnosis of pituitary deficiency.

The results of laboratory tests conducted during the period of observation may be recounted. Soon after treatment was started with the pituitary fraction, insulin tolerance was measured with the following results: 0.01 unit of insulin per kilo body weight (total 0.64 units), given intravenously, led to severe hypoglycemic symptoms within 20 minutes, at which time the capillary blood sugar was 70 mg. This sensitivity to insulin was present throughout the entire period of 20 months. The glucose tolerance, however, gradually increased and at the end of 1 year was as follows: fasting, 90 mg. per 100 cc.; ½ hr., 142 mg.; 1 hr., 150 mg.; 2 hrs., 40 mg.; 3 hrs., 122 mg.; 4 hrs., 100 mg. Specific dynamic action tests at no time revealed any departure from the normal. This was also true of the estimations of serum calcium, phosphorous, total proteins, albumin and globulin. The blood cholesterol, while slightly above average (227-231), did not vary appreciably.

Basal metabolic rates were determined repeatedly. There was a slight rise after the first week of pituitary treatment followed by a sharp fall. These persistently low values ranging from —30 per cent to —40 per cent are shown in chart 1. Check roentgenograms of the calvarium (3-8-35) presented the same findings as at the beginning of the observation with the possible exception of a more densely calcified area within the sella turcica.

DISCUSSION

The patient presented roentgenographic evidence of early acromegaly, namely, a thickened bony calvarium, large sella, prominent frontal and zygomatic bones, large frontal sinuses, large hands with tufting of the distal phalanges and hooking of the thumb. At no time during our period of observation, however, were there symptoms of active acromegaly. It was assumed that this disorder had been active sometime prior to the onset of the clinical manifestations herein described and were inactivated by the acute illness of March, 1931. While the nature of this illness remains obscure, the site of the pathological lesion was probably in the neighborhood of the hypothalamus, as evidenced by the transient diabetes insipidus which later ensued. The present slowness of speech and blankness in facial expression may well be residuals of that episode.

[2] APE (A), anterior pituitary extract supplied by the Department of Biological Research, University of California, Berkeley, California. APE (B), anterior pituitary extract supplied by the Research Department of E. R. Squibb and Sons, New Brunswick, N.J.

The outstanding symptoms of the chronic illness which followed this acute episode could in no way be attributed to active acromegaly. On the contrary, these symptoms, together with a high glucose tolerance, low oxygen consumption rate, hypotension and the presence of a calcified shadow within the sella, pointed to hypofunction of the anterior pituitary. The validity of this reasoning was borne out in the therapeutic response when alkaline extracts of the anterior lobe were administered. The most striking effect was that upon weight. Weight gain was consistent while the patient was receiving the extracts and weight loss always ensued when they were withdrawn. The weight has now apparently reached a plateau from 10 to 15 pounds below the theoreti-

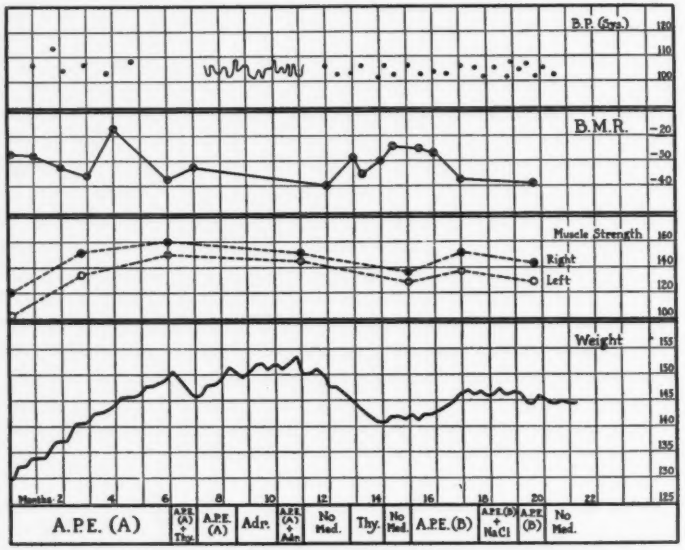


Chart 1. Showing effect of treatment on B.M.R., blood pressure, muscle strength and weight. APE== anterior pituitary extract. Thy.=thyroid (½-1 grain, daily). Adr.=adrenal cortex by mouth (2-3 gm. fresh gland equivalent, daily).

cal optimal. A definite increase in strength was noted from the first. Although inadequately measured, it followed roughly the weight curve (chart 1). There was, in addition, an apparent increase in the tone and volume of the muscles.

A striking sensitivity to insulin was demonstrated. This phenomenon is felt to be due to a dearth of the hypophyseal contrainsular fraction or buffer substance in contradistinction to hypoglycemia of purely pancreatic origin. The insulin-sensitivity test in the latter condition does not lead to hypoglycemic shock and may be employed in differentiating between the two. Likewise, anorexia is common in hypopituitary states, whereas, excessive appetite is common in hyperinsulinism. Originally, the glucose tolerance was definitely increased and anorexia was present. Following 4 to 5 months of therapy with the pituitary extracts, a decrease in the glucose tolerance and a concomitant increase in the appetite was noted.

The blood pressure was not altered by any form of treatment. A glycerin extract of adrenal cortex in relatively large doses was administered orally alone and in conjunction with the anterior-pituitary extract. Daily blood pressure readings under basal conditions at the same hour and in the same position during this period revealed no appreciable change. According to Hoskins (5), the adrenal preparation, when given in comparable doses to schizophrenic patients, usually resulted in a definite increase in blood pressure. The basal metabolic rate rose slightly after the first week of treatment with the pituitary extracts but as promptly subsided to a level lower than that encountered in the beginning. Small doses of thyroid alone elevated the basal metabolic rate to around —18 per cent but weight loss and aggravation of the subjective symptoms ensued.

SUMMARY

A case of acromegaly followed by pituitary calcification and subsequent emaciation is reported. The symptoms, signs and laboratory findings leading to a diagnosis of 'fugitive acromegaly' are discussed. Alkaline extracts of the anterior pituitary were employed as diagnostic and therapeutic measures. The carbohydrate tolerance was lowered but the basal metabolic rate and blood pressure remained unaltered throughout the experiment. The patient regained weight, strength and a sense of well-being and with periodic doses of the extract continues to maintain at a fair level of normality.

REFERENCES

1. Simmonds, M.: Deutsche med. Wchnschr. **40:** 322. 1914.
2. Calder, R.: Bull. Johns Hopkins Hosp. **50:** 87. 1932.
3. Bailey, P. and H. Cushing: Am. J. Path. **4:** 545. 1928.
4. Willoughby, D.: Research Quarterly, Am. Phys. Educ. Assn. **3:** 48. 1932.
5. Freeman, H. and R. G. Hoskins: Endocrinology **18:** 576. 1934.

HYPERTROPHY OF THE TESTES WITH SYMPTOMS OF HYPERORCHIDISM[1]

J. K. FANCHER
ATLANTA, GEORGIA

Enlargement of the human testes, as differentiated from sexual precocity in which the penis is involved (1), is commonly attributed to syphilis, tuberculosis or tumor. Simple hypertrophy has not been demonstrated.

The patient to be described presented hypertrophy as well as the syndrome associated with over-production of the testicular hormones. A biopsy, unilateral orchidectomy and transplantation confirmed the diagnosis.

Case report. M.D. was an American male mechanic of 20 years. He was seen in jail because of stealing and wrecking various automobiles. The essential factors in his history were a birth weight of 11¼ lbs. with a difficult labor of 3 days without instrumentation. The first tooth appeared at 5 months. He had the usual diseases of childhood. A ruptured appendix and infected tonsils were surgically treated at age 13. Influenza at age 17 was followed the same year by operation for left hydrocele. Two years later a right hydrocele was repaired. Both hydroceles were unusually large. Three head injuries are recorded. One at age 16 when the patient struck his head in a concrete swimming pool and became unconscious. At age 17 he was struck with a brick and later with a hammer, but did not lose consciousness. The hypertrophy began at 12 years. Steady increase was noted in the size of both the scrotum and the testes until after the hydrocele operations. One medical examiner advised the patient that he probably had cancer.

The personality was reversed. He had been an affectionate and obedient child but changed during adolescence, growing worse until his activities brought him into the hands of the law. He admitted coitus on several occasions. He was very sensitive about his enlargement and lived in extreme moods. His employer found his work satisfactory as a mechanic. Signs which augured the onset of an abnormal period were: dilated pupils; a desire to be unmolested; irritability even to the point of violence; at times staring vacantly into space; poor appetite and groaning in his sleep. At times he was perfectly normal in appearance and actions. "Like a wave" over him would come the impulse that he must do something. He described this uncontrollable feeling as "terrible." To overcome this desire he drank whiskey or ate veronal. Under the influence of each of these he had on several occasions stolen and wrecked automobiles. The police recognized that the boy was not vicious and did not press charges.

The patient was exceptionally muscular (fig. 1, *A*). His voice was deep, well modulated and pleasant, and his personality was attractive. He was 71 inches in height and weighed 188 lb. The estimated weight was 158 lb. He wore a No. 11 shoe and 15½ collar. He had a moderately heavy beard. His hands were large, with normal nails, and he was fairly well proportioned although the torso exceeded the

[1] Read before the Nineteenth Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N.J., June 11, 1935.

long measurement. The scrotum was very large and distended by the testes which were about the size of goose eggs. There was no evidnce of scrotal fluid. The blood Wasserman test was repeatedly negative in reaction and the blood chemistry was not unusual. The basal metabolic rate was —13 per cent. Roentgen and neurological study of the cranium showed nothing abnormal. A biopsy from the left testis showed no evidence of true inflammatory or neoplastic structures, the entire process being apparently one of marked hyperplasia.

The patient acquired a long police record during the following 3 years. He also had surgery for acute pancreatitis and cholecystitis. A period of 9 months was spent in the state hospital for the insane with a manic-depressive diagnosis. He finally submitted to right orchidectomy. Two-thirds of the testis was transplanted into the abdominal wall of a eunuchoid patient (fig. 1, *B*) of the same age with striking stimulation for 6 months. The donor was relieved of his symptoms.

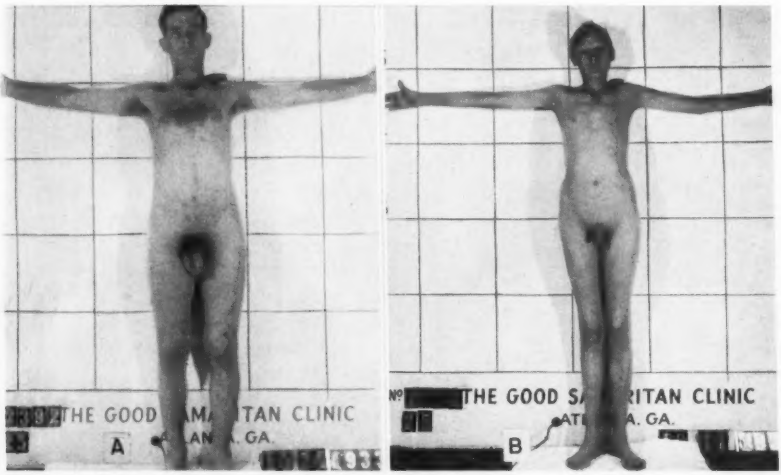


Fig. 1. *A*, Patient M.D., testicular hypertrophy. Biopsy had been made and the scrotum clipped before the photograph was made. Note the exaggeration of male characteristics. *B*, eunuchoid type of hypogonadism. The patient was the recipient of two-thirds of the right testis of the patient shown in *A*. Definite stimulation followed.

The symptoms of hyperorchidism are unknown. The probable symptoms are based upon clinical knowledge of the opposite state, testicular hypofunction. Sajous concluded that such manifestations should be: abundant facial hair, marked lack of mammary development, heavy musculature and great strength, combativeness, and sexual proclivities above the average. This patient presented all these expected findings plus enlarged testes, deep voice and personality changes. In addition the biopsy, orchidectomy and transplant offer substantial corroboration.

In contrast to his previous history, the patient has had no contact with the police since operation 2 years ago.

REFERENCES

1. Lisser, H.: In Blumer's Bedside Diagnosis, III. 302. 1928.
2. Rowe, A. W. and C. H. Lawrence: Publications from the Robert Dawson Evans Memorial, P. 595. 1929.
3. Sajous, L. T.: In Tice Practice of Medicine, VIII. 188. 1926.

THE TREATMENT OF PITUITARY INFANTILISM WITH ANTERIOR PITUITARY EXTRACT

MAX M. GOLDBERG
From the Department of Medicine, Touro Infirmary
NEW ORLEANS, LOUISIANA

The purpose of this paper is to report the changes which occurred in a patient in whom the cardinal symptoms of pituitary infantilism (undergrowth, absence of sex characteristics, late epiphyseal union) were present, co-incident with the administration of anterior pituitary extract (Squibb). The infantilism was of the Levi-Lorain type.

Case report. L. J., (fig. 1, *A*) male, aged 18½ years, entered the medical clinic April 26, 1935, complaining of weakness and fever of several months duration. The past history was not significant except that his mother stated that he had not grown since he was 10 years old. The voice changes had never taken place and the patient still had a childish voice when he entered the clinic. He stated that erection or ejaculation had never occurred and that he had never successfully masturbated. Two younger brothers, ages 12 and 16, were of normal height and weight.

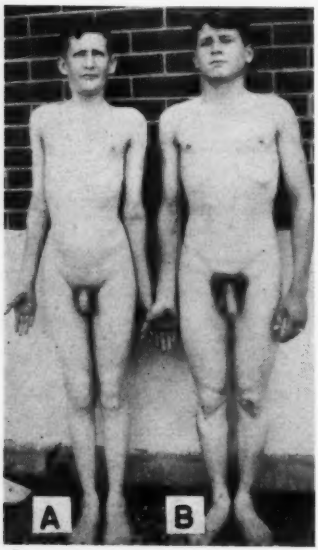


Fig. 1. *A*, The patient, aged 18½ years; height 59.4 in.; weight 79 lb. *B*, The patient's brother, age 16½ years; height 61.5 in.; weight 109.5 lb.

He had complained mainly of weakness and lack of energy and stated that he thought he had fever, although his temperature was always found to be subnormal in the clinic.

Upon physical examination, the characteristic features were the small stature, the old-man facial appearance (progeria), the girlish voice and the lack of axillary and pubic hair. A few scant hairs were found at the base of the penis. The penis was a small normal; the testicles were small and in the scrotum. The height was 59.4 in., the span 62.5 in., the weight 79 lb.

The routine laboratory examination of the urine and the blood revealed normal findings. The Wassermann test reaction was negative. The B.M.R. was —7 per cent. The radiologic examination of the left elbow showed open epiphyses; that of the left wrist and fingers showed open epiphyses.

Course and treatment. The patient was given anterior pituitary extract (Squibb) subcutaneously 3 times a week, beginning April 29, 1935. The first 2 doses were of 0.5 cc. each, the third, 0.75 cc., the next 4 of 1.0 cc. each, the next 6 of 1.2 cc., the

next 3 of 1.5 cc., and the next 20 of 1.0 cc. In all he received 36 injections, or a total of 37.5 cc.

The statural changes are summarized in the table. The figures for a younger brother (fig. 1, *B*) are shown for comparison.

On May 27, after 13 injections had been given, the patient had an erection and ejaculation for the first time in his life, during sexual intercourse. Subsequently sexual intercourse and masturbation occurred normally.

On May 29, he stated that he no longer felt weak, he had more energy and felt like getting up in the morning. On June 5, the patient complained of a backache

Patient L.J.	4/26/35	5/22/35	6/5/35	9/4/35	9/30/35	1/3/36
Height, in.	59.4	59.9	60.0	61.4	61.4	62.5
Span	62.4	62.5	62.5	63.8	63.8	64.5
Pubis to floor	31.4	31.5		32.3	32.5	33.4
Head	19.5	19.5	19.5	20.3	20.3	
Chest	25.5	25.5	27.0	27.5	27.5	
Waist	23.0	23.5	23.5	25.3	25.5	
Weight, lb.	79.0	80.5		85.0	85.5	89.5

Brother, R. J.	4/26/35	9/16/35
Height, in.	61.5	61.5
Span	65.8	66.0
Pubis to floor	31.8	32.0
Head	21.3	21.3
Chest	31.8	32.0
Waist	27.0	27.0
Weight, lb.	109.5	108.5

beginning several hours after the injection and lasting for several hours. Also he complained that the erections were prolonged, 5 to 10 minutes after ejaculation. Both of these symptoms were relieved by reducing the dose from 1.5 cc. to 1.0 cc.

Treatment continued throughout June, July and August, 3 cc. a week. During the latter part of August and the first part of September voice changes took place, the voice becoming crowing and changing suddenly in pitch during conversation. Definite stimulation of pubic hair growth and penile growth occurred. Masturbation and sexual intercourse occurred normally. Treatment was stopped on Sept. 4, at which time he had grown 2 inches. Radiologic examination showed no changes in the epiphyses at this time. The younger brother showed no growth during the period. On Jan. 3, 1936, a checkup showed that growth was continuing without treatment.

SUMMARY

Coincident with administration of 37.5 cc of anterior pituitary extract (Squibb) over a period of approximately 4½ months, a male patient, exhibiting the cardinal symptoms of pituitary infantilism of the Levi-Lorain type, gained 2 inches in height and exhibited definite stimulation of the primary and secondary sexual characteristics.

Growth continued following the cessation of treatment, approximately 1⅛ inches in 4 months. During the period of treatment he gained 6 lb. and subsequently 4½ lb.

PITUITARY INFANTILISM WITH DIABETES MELLITUS

DANIEL L. SEXTON AND FRITZ NEUHOFF
From the Endocrine and Diabetic Clinics, Firmin Desloge Hospital
ST. LOUIS, MISSOURI

Following the work of Houssay and his collaborators (1), Barnes and Reagan (2), and others, little doubt remains that the anterior lobe of the pituitary forms a substance the action of which is antagonistic to insulin, and evidence tends to show that this diabetogenic substance is contained in active growth extracts. This is manifested clinically in acromegaly. Cushing (3) has stated that glycosuria and hyperglycemia occur in acromegaly in about the ratio of 1 to 4.

As early as 1911 Goetsch, Cushing, and Jacobson (4) called attention to increased tolerance to carbohydrates in hypopituitarism. Turner (5) and Schaefer (6) working separately with pituitary dwarfs found the fasting blood sugar within normal limits. One of us (D.L.S.) has found a low normal fasting blood sugar to be the rule in dwarfism. Because of the relative infrequency of glycosuria and hyperglycemia associated with pituitary dwarfism, the following case is reported.

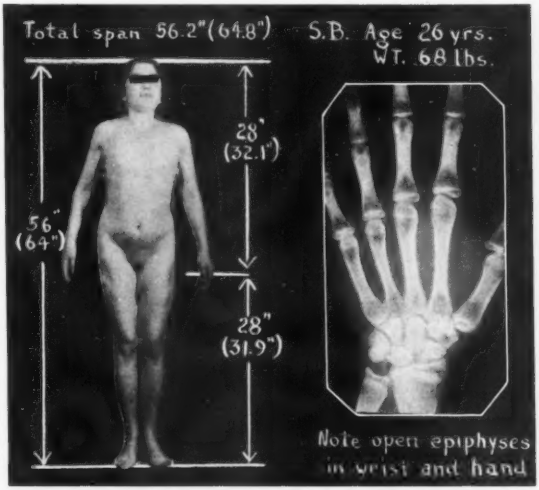
Case report. S.B., a Jewish girl 25 years of age, entered Firmin Desloge Hospital on April 2, 1934 complaining of loss of 20 lb. in weight during the previous 10 months, retarded statural development, failure to menstruate, absence of secondary sex characteristics, painful and involuntary urination on occasions when excited, weakness, nervousness, fatigue, and constipation.

The patient was an only child, born of parents of normal stature. Her maternal grandmother had been treated for diabetes for years. A full term baby, she was said to have weighed 2.5 lb. at birth. She was breast fed for the first 6 months. Dentition, walking, and talking occurred at the normal times. She suffered from persistent vomiting and diarrhea throughout the first year of life. At the end of her first year she was very small although her exact weight was not recalled.

The common childhood diseases had occurred. At the age of 16 she was ill with malaria. She repeatedly sought aid for her underdevelopment, and on one such occasion, at about the age of 17 years, desiccated thyroid and anterior pituitary substance were prescribed and taken orally without effect. It was shortly thereafter that Doisy isolated the estrogenic principle from pregnancy urine. This patient became the subject for clinical trial of this hormone (estrogen) under the supervision of Dr. George Gellhorn. Given 5 injections of this preparation weekly over a period of about 1 year, she claimed to have had slight vaginal bleeding on 3 occasions at irregular intervals during the last 6 months of treatment. At no other time in her life had she noted vaginal bleeding. At the end of a year the injections were discontinued and transplants of 2 pituitaries from young cattle were made in the subcutaneous tissues of her thigh by Dr. Gellhorn. The transplants were repeated after 2 months with no untoward reaction. No record of her height was kept at that time,

but according to the patient's statement, she grew about 1.5 inches during the entire period over which she had received the estrogenic principle and the pituitary transplants.

Fasting blood sugar at the time of these operations were 182 mg. per cent on both occasions and glycosuria was present. Frequency of urination and polyuria of 3-months' duration were other complaints listed at the time of these hospital entrances. Although she had consulted physicians a number of times before and had had repeated urinalyses, no glycosuria was ever reported to her. When the diabetes was first discovered, she was placed on a diabetic régime consisting of diet and insulin therapy to which she adhered until 1 year ago when of her own accord she discontinued all treatment. For several months before entering Desloge Hospital she had been aware of glycosuria but had done nothing to overcome it. Her weight



had decreased 20 lb. in 10 months, and weakness and fatigue had assumed great proportions. On occasions when nervous, urinary incontinence had occurred, but there had been no polyuria or polydypsia at this particular time. There was no evidence of sexual interests.

On physical examination the patient was highly emotional and of an extremely nervous temperament which was poorly controlled. Her height was 56 inches, and her weight was 68 lbs. She had normal body dimensions, the upper and lower measurements being exactly equal. The total span was 56.2 inches. The pulse rate was 84; the blood pressure was 96/66; and temperature was 98.2°. She gave the general impression of a well-formed immature girl except for the facies which depicted her true age. The lack of sexual development, both primary and secondary, was striking; the breasts were represented by a slight fullness with small nipples; there was no auxillary hair growth and the growth of pubic hair was sparse. The gums showed marked pyorrhea alveolaris and there were many dental replacements.

Urinalysis, single specimen, revealed a specific gravity of 1.030, sugar 3+ and acetone and diacetic acid positive. A 24-hour specimen amounted to 2700 cc., with a specific gravity of 1.028, sugar 4+, acetone 2+, and diacetic acid present. The

blood morphology was normal with the exception of a slightly reduced hemoglobin (78 per cent). The Wassermann and Kahn tests were negative. The blood sugar was 165 mg. per cent. A roentgenogram of the lateral skull revealed a small but normal sella turcica. Roentgenograms of the osseous system revealed incomplete union of the epiphyseal centers with the diaphyses.

Dr. William H. Vogt reported the gynecologic examination as follows. "The external genitals are poorly developed. There is a small amount of hair growth. The labia majorae present a glistening white appearance. The labia minorae are absent (entirely atrophic) except where they form the prepuce and frenulum of the clitoris. The introitus is narrowed, forming a scar-like ring and making digital palpation of the pelvic organs impossible. By rectal palpation, the uterus shows atrophy and retroflexion. There are some enlarged inguinal glands on both sides but more marked on the right side. The diagnosis is leuko-kraurosis."

A psychiatric examination by Mr. F. T. Harrington was reported as follows. "The patient's chronological age is 25 years; her mental age is 17 years, 11 months. She is classified in the superior mental group, her IQ being 112. The patient has an impressive vocabulary and passed 3 tests in the superior adult group and all of the tests of the average adult group. She is markedly introverted and needs the psychic stimulus of success in some line of work."

Course. Treatment was directed toward the hyperglycemia and glycosuria (under the direction of F.N.). Her diet prescription was protein 64 gm., carbohydrate 110 gm., and fat 120 gm. Insulin was given in increasing doses until, at the end of 9 days, it was 23 U. Urine then showed 2+ sugar but was free from acetone and diacetic acid. The blood sugar had increased to 192 mg. per cent. No attempt was made to stimulate sexual development or growth.

The patient remained in the hospital only a short time after glycosuria was controlled. She returned to the clinic where, on supposedly constant dosages of insulin and regulated diet, different hormones were injected to note their effect on the blood sugar level. It was discovered that she was not coöperating and, after several unsuccessful attempts to obtain coöperation, these experiments were abandoned. Rarely was the urine sugar-free. Her final diet prescription was protein 63 gm., carbohydrate 110 gm., fat 110 gm. The prescribed dosage of insulin was 36 U. daily. Her weight after 1 year's observation was 84½ lb., an increase of 16½ lb.

DISCUSSION

Reports of glycosuria and hyperglycemia with classical hypopituitarism have appeared before. Shapiro and Kliatshko (7), Kenyon (8) and Strecker (9) have reported cases of clinical hypopituitarism showing decreased tolerance to sugar, but in each instance a pituitary tumor was found. John (11) reported 5 cases of clinical hypopituitarism, without tumor, which showed glycosuria and hyperglycemia.

That the case herewith reported was not primarily one of diabetic infantilism is borne out by the fact that the patient was 19 years of age before glycosuria was discovered. Since she had consulted physicians a number of times previously, it is hardly likely that glycosuria would have been repeatedly overlooked. Furthermore, there were no symptoms of diabetes mellitus until shortly before the time when glycosuria and hyperglycemia were discovered. Infantile statural and sexual development without demonstrable organic cause, plus the finding of delayed union of the epiphyseal centers (normally epiphys-

eal closure occurs between 16 and 18 years in the female) constitute the cardinal signs of pituitary dwarfism. Diabetes in this case is believed to be of true pancreatic origin, i.e., due to a deficiency in insulin, and its occurrence is considered to be entirely independent of the pituitary syndrome.

SUMMARY

The case is reported of a girl of 25 years having diabetes of late onset and presenting a classic picture of pituitary infantilism (dwarfism). The case is paradoxical in that hypopituitarism is commonly associated with augmented sugar tolerance.

REFERENCES

1. Houssay, B. A. and A. Biasotti: Endocrinology **15:** 511. 1931.
2. Barnes, B. O. and J. F. Reagan: Endocrinology **17:** 522. 1933.
3. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalmus, and Parasympathetic Nervous System, Chas. C. Thomas, Springfield and Baltimore, 1932.
4. Goetsch, E., H. Cushing and C. Jacobson: Bull. Johns Hopkins Hospital **22:** 165. 1911.
5. Turner, H. H.: Personal Communication.
6. Schaefer, R. L.: Endocrinology **20:** 64. 1936.
7. Shapiro, S. and M. G. Kliatshko: Arch. Neurol. & Psychiat. **15:** 85. 1926.
8. Kenyon, J. H.: Arch. Neurol. & Psychiat. **26:** 656. 1930.
9. Strecker, E. A.: M. Clin. North America **14:** 835. 1931.
10. John, H. J.: Endocrinology **9:** 397. 1925.

CLINICAL AND LABORATORY NOTES

A SIMPLE METHOD OF HYPOPHYSECTOMY IN THE DOG*

RICHARD J. BENNETT, JR.

A new method of hypophysectomy in the dog has been devised and found most satisfactory. In using this method the removal of the pituitary gland is complete and the procedure is performed in a relatively short time, the average time required being 9 minutes.

In studying the dog's skull, a new plan of approach to the pituitary gland was evolved. By forcing a sharp pointed instrument through the pituitary fossa from the inside of the skull, it was found that the point emerged in the nasopharynx exactly between and directly vertical to the hamular processes of the pterygoid (fig. 1. A). A metal guide was then constructed which fitted snuggly over the hamular processes of the pterygoid and acted as an accurate guide to the pituitary fossa from the nasopharynx. This guide was perfected for use on dogs weighing from 10 to 20 kg. (fig. 1, B).

Working through the mouth of the dog with the aid of this guide proved difficult. Experience in a large surgical practice where cysts of the thyroglossal duct are removed through the structures in the midline of the submandibular region and tongue with little bleeding, suggested the possibility of working through the same anatomical region of the dog. The steps in the operative technic for removal of the pituitary gland are as follows:

1. The dog is given full ether anesthesia and then placed on the operating table in the same position as for an abdominal operation.

2. The mouth is held open with a mouth gag.

3. A curved metal intratracheal tube for anesthesia is placed in the trachea in such a manner that the tube emerges from the side of the mouth leaving the midline clear for the operative procedure.

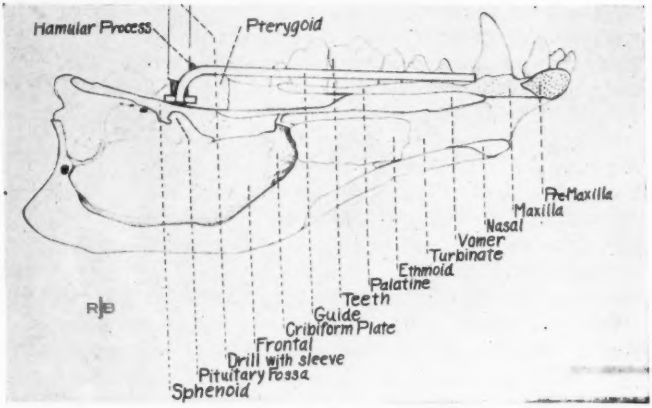
4. The tongue is pulled well out of the mouth and fixed to the skin of the lower jaw by means of towel clips.

5. The soft palate is split down the center from its free edge to its union with the hard palate. The 2 portions are retracted laterally exposing the base of the sphenoid and the hamular processes of the pterygoid. The nasopharynx is painted with 2.5 per cent tincture of iodine.

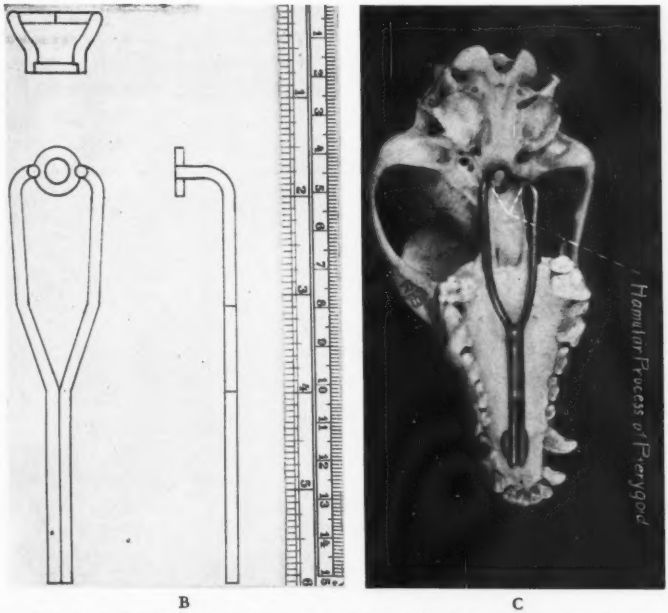
6. The metal guide is slipped over the hamular processes of the pterygoid and held in the midline at its anterior extremity by the assistant (fig. 1, C).

7. A point on the skin in the submandibular region immediately above the center point of the guide is prepared with 2.5 per cent tincture of iodine. A sharp scalpel is held in the midline vertical to the plane of the hard palate above this point with the width of the blade in the longitudinal axis of the skull. After making certain that the scalpel is in the right position, the incision is carried through

* This work was carried out in the Department of Physiology, University of Alberta, Edmonton, Alberta.



A



B C

Fig. 1. A. Longitudinal vertical section of the skull of the dog showing the metal guide in place. B. Diagrammatic drawing showing construction of metal guide. C. Dog skull with mandible removed to show metal guide in place in relation to hamular processes of the pterygoid.

the midline of the submandibular region and the tongue. If a sufficiently large blade is used, one thrust of the scalpel is all that is necessary to admit the quarter-inch short bevel drill and its protecting sleeve. The protecting sleeve is necessary to prevent the drill from entering the pituitary fossa too far and thus injuring the brain.

8. The point of the drill is inserted through the incision in the submandibular

region and tongue and is then placed in the circular portion of the guide just over the pituitary fossa. A carpenter's brace is used to hold the drill.

9. Making certain that the brace is vertical to the plane of the hard palate, it is turned slowly. After about 10 complete revolutions, the drill drops into the pituitary fossa and the sleeve around the drill makes contact with the guide. A quarter-inch hole has then been made into the pituitary fossa.

10. The brace, drill, and guide are then removed.

11. A curved suction tip is quickly placed through the quarter-inch hole in the pituitary fossa and the pituitary gland is easily removed.

12. A small piece of softened bone wax is quickly forced into the quarter-inch hole to control hemorrhage.

13. The intratracheal anesthesia tube is removed and the soft palate is joined with a running linen suture.

14. The skin incision in the submandibular region is closed with 1 linen suture, and the operation is finished.

Summary. A satisfactory method of complete hypophysectomy in the dog has been devised which requires an average of 9 minutes for completion. The approach to the pituitary fossa is made certain by the use of a metal guide fitted over the hamular processes of the pterygoid. A carpenter's ordinary brace and drill are used, the drill being passed through the submandibular region and tongue to enter the guide. The gland is completely removed by means of a suction tip.

ON THE EVALUATION OF THE POTENCY OF ESTROGENIC SUBSTANCES*

S. C. FREED AND S. SOSKIN

Many different, though chemically related, substances have been shown to possess significant estrogenic activity as measured by vaginal cornification in rats. The latter reaction, however, is but one of several produced by the estrogenic substances. Practical considerations in connection with the ease of the experimental procedure have led to the general use of the vaginal smear method as the basis for comparison of the physiological activity of the estrogenic substances. This convention seems unwarranted in view of the lack of evidence that there is any constant quantitative relationship between vaginal cornification and other, perhaps more significant, physiological effects occurring in experimental animals after injection of estrogenic substances. Indeed, unless such a relationship can be shown to exist, it would seem desirable from the point of view of the ultimate selection of these materials for use in the treatment of human sex disorders, to choose a method of assay more closely related to the outstanding phenomena of the human sex cycle. In this regard we wish to report the effects produced by different estrogenic substancs on the pituitary-ovarian relationship in rats.

Method and Results. One of the most fundamental properties of estrin is its influence on the pituitary gland. The commonly accepted conception of the regulation of the sex cycle is based on this relationship.[1] It has been shown repeatedly that the continued injection of estrogenic substance over prolonged periods produces an atrophy of the sex organs through inhibition of pituitary activity.[2, 3, 4] The following results were obtained from a comparison of the gonad inhibiting activity of the keto and trihydroxyestrins, contained in pregnancy urine, with synthetic dihydroxyestrin-benzoate.

An extract of pooled pregnancy urine containing both the keto and trihydroxyestrins was injected into adult female rats. The daily dose was 5 R.U. and the injections were conducted over a period of 30 days.† The ovaries from the treated animals averaged 70 mg. in weight, those of the controls, 80 mg. Grossly and microscopically the ovarian structures appeared normal which indicates that there was only slight inhibition of pituitary activity under these conditions.

A markedly different effect was seen, however, when dihydroxyestrin-benzoate was used.‡ Injections of 3 R.U. daily over a period of 25 days resulted in a severe atrophy of the ovaries. The follicular apparatus was underdeveloped and corpora lutea were absent or in the final stages of atresia. These ovaries averaged 28 mg. and many resembled those from normal infantile rats.

---

[1] Moore, C. R., and D. Price: Am. J. Anat. 50: 13. 1932.
[2] Allen, E., and E. A. Doisy: Am. J. Physiol. 69: 573. 1924.
[3] Doisy, E. A., I. Curtis and W. D. Collier: Proc. Soc. Exper. Biol. & Med. 28: 885. 1930.
[4] Meyer, R. K., S. L. Leonard, F. L. Hisaw and J. Martin: Proc. Soc. Exper. Biol & Med. 27: 702. 1930.

* From the Department of Metabolism and Endocrinology, Michael Reese Hospital, Chicago, Illinois. Aided by a grant from the Committee on Scientific Research of the American Medical Association.

† The estrogenic activity in the crude P.U. extract as assayed on castrated adults is mainly due to ketohydroxyestrin, only about 1 per cent is from the trihydroxyestrin.[6] There is at least an equal amount by weight of the latter present in P.U., however.

‡ Progynon B, obtained through the courtesy of Dr. G. Stragnell, Schering Corporation.

Summary and Conclusions. Our results demonstrate that closely chemically-related estrogenic substances differ markedly in their ability to suppress the pituitary of the adult female rat when injected in comparable doses based on their ability to cause vaginal cornification. This difference is in agreement with the work of David et al,[5] who showed that in a series of estrin compounds, compared on vaginal estrus units, there was considerable individual variation in activity on smooth muscle or epithelial tissue. Similarly, related male sex hormones compared on the basis of comb growth activity vary extremely in their ability to stimulate the rat's accessory sex organs.[6]

It is concluded that the potency of an estrogenic substance as regards vaginal cornification bears no constant relationship to its potency as regards other important physiologic properties. An assay of estrogenic substance by the vaginal smear method alone is, therefore, not a reliable indicator of its potency as regards other physiologic properties, or of its possible value in therapeutics.

FURTHER INVESTIGATION OF THE HORMONE CONTENT OF SALIVA USING THE FEMALE BITTERLING TEST*

ABNER I. WEISMAN

Much investigation has been carried on in search of sources of excretion and secretion of the so-called 'sex hormones.' It is now a well established fact that the two sexes excrete both the male and female hormones in the urine. These hormones can also be demonstrated in the blood stream. With all this investigation, little attention has been paid to the relationship of the secretions of the salivary glands to the sex hormones. In January 1936, Weisman and Yerbury[1] reported a series of experiments using mice as the test animals and came to the conclusion that neither the estrogenic hormones nor the anterior pituitary-like hormones were to be found in saliva.

Recently there has come into use a new laboratory animal, the female European bitterling (Rhodeus amarus), which possesses an external ovipositor. The fish during its normal breeding season extrudes the ovipositor to a length of 15 to 25 mm. and thereby deposits its eggs. It has been shown by many investigators[2, 3, 4] that the female bitterling can be stimulated to lengthen its ovipositor at will by the addition of certain chemical stimuli which are hormonal in nature.[5] There had been some discussion as to exactly which hormone was responsible for the ovipositor reaction, and it remained for Kleiner, Weisman and Mishkind,[6] to definitely show that the causative factors were the male hormones. Further work by the same authors confirms and corroborates their original findings.

Experimental. Using the female bitterling test for male hormone, and following the technique devised by Kleiner et al, salivas of normal males, normal females, and pregnant females were tested. In the original technique performed with urine, the amount of substance used was 4 cc. per liter of water using 4 liters per tank. Since saliva has a much lower specific gravity than has urine it was deemed necessary to

[5] David, K., J. Freud and S. E. DeJongh: Biochem. J. **28**: 1360. 1934.
[6] Deansely, R., and A. S. Parkes: Biochem. J. **30**: 291. 1936.
* From the Endocrine Clinic of the Metropolitan Hospital, New York.
[1] Weisman, A. I., and C. C. Yerbury: Endocrinology **20**: 103. 1936.
[2] Kanter, A. E., C. P. Bauer, and A. H. Klawans: Am. J. Obst. & Gynec. **31**: 764. 1936.
[3] Fleischmann, W., and Susanne Kann: Arch. f. d. ges. Physiol. **230**: 662. 1932.
[4] Kleiner, I. S., A. I. Weisman, and H. Barowsky: J.A.M.A. **104**: 1318. 1935.
[5] Kleiner, I. S., A. I. Weisman, and D. I. Mishkind: Proc. Soc. Exper. Biol. & Med. **34**: 367. 1936.
[6] Kleiner, I. S., A. I. Weisman, and D. I. Mishkind: J.A.M.A. **106**: 1643. 1936.

use more than the amounts originally suggested. Therefor 16 cc. of saliva per liter was used in four liters of water. Specimens of saliva were obtained from 10 normal males, 10 normal females, and 15 pregnant females. A positive reading was understood to be a lengthening of the ovipositor of at least one out of two fish in the tank containing 4 liters of water, within 48 hours according to the scale devised by Kleiner et al. In all the 35 specimens tested upon the bitterlings there was not one positive result. This indicates that in 64 cc. of salivas there is not one bitterling unit.

Discussion. Having previously shown that the estrogenic and anterior pituitary-like hormones were absent from saliva, it is now shown that the male hormones are also lacking in the various salivas tested. This result confirms the previously expressed opinion that the salivary glands are not a pathway of sex hormone excretion.

Summary. Salivas from normal males, normal females, and pregnant women, were tested upon the female bitterlings for the presence of the male hormones. No male hormone was found in any of the saliva tested.

DATING ENDOCRINE SUBSTANCES: A PLEA FOR FRESH PRODUCTS

ISRAEL BRAM

Prescribing endocrine products without insistence on their freshness is a common flaw in glandular therapy. Thus we subject ourselves to erroneous impressions regarding the efficacy or futility of the products employed, unwittingly denying many patients the possible benefit from the use of fresh products. Indeed, our indifference to this matter has subjected an unknown percentage of patients to acute illness from poisoning. The following case histories will exemplify.

For J.M., a girl of 13, was prescribed a capsule containing whole pituitary substance. Two days later, after having taken 5 or 6 capsules, she began to experience pain and tenderness in the abdomen, anorexia, nausea, and frequent bowel movements. Careful inquiry into dietary habits revealed no flaws. The remedy was discontinued for a few days and when the symptoms complained of had ameliorated, the capsules were resumed. After taking the third capsule, the gastrointestinal symptoms recurred. Conversation with the druggist revealed that the pituitary substance had been standing on his shelves for over a year, the bottle having been opened only once before to fill a prescription. New capsules filled with a fresh product produced no complaints.

Mr. N.M., 36, was given a prescription calling for adrenal substance in 3-grain capsules. Several days later he stated that the capsules were causing loss of appetite, abdominal discomfort, weakness and distressing diarrhea. He, too, was ordered to discontinue the capsules until the symptoms had disappeared, then to resume them and report any return of symptoms. Five days later, shortly after taking a second capsule, the symptoms recurred. The patient now discontinued the remedy and the druggist was consulted. In this case it was discovered that the age of the product was about 18 months. The resumption of the capsules filled with a fresh product occasioned no return of gastrointestinal symptoms.

While there is considerable doubt in the minds of many physicians whether the oral administration of either pituitary substance or desiccated adrenal is efficacious, such doubt is beside the point in the present connection: the preparations were prescribed and the results were as stated. Whether wisely or not such preparations are in frequent use.

A number of other cases of like nature have come to attention in recent years. It would seem that the assumption that endocrine products are always fresh is a mistake. Many patients who should return regularly to the physician for a check-up disappear from his view because of the harm wrought by a prescription containing putrified endocrine substance, the patient preferring to change physicians, or to discontinue medical attention.

If glandular opotherapy is to progress, constant vigilance must be exercised regarding the reliability of the remedies employed. It is illogical to accept the premise that organic substances are immune to deterioration as many druggists and even physicians imply by their indifference to the age of these products. The determination of the potency and safety of glandular substances of varying age should engage the serious attention of investigators in this field. It would be reasonable to expect that in the very near future the medical profession will insist that all glandular products be properly dated by the manufacturer as to their approximate time of expiration of freshness and usefulness.

CURRENT ENDOCRINE LITERATURE

COLLABORATORS

Fuller Albright
I. Andrussier
Wayne J. Atwell
Geoffrey Bourne
Israel Bram
John C. Burch
John C. Donaldson
Maurice H. Friedman
Murray B. Gordon
Arthur Grollman
Frank A. Hartman
E. C. Hamblen
F. C. Koch
Edward Larson
J. T. Lewis
Joseph M. Looney
Warren O. Nelson
J. P. Pratt
A. T. Rasmussen
Elmer L. Sevringhaus
L. B. Shpiner
D. L. Thomson
R. L. Zwemer

BOOK REVIEWS

Glandular Physiology and Therapy. A Symposium. Prepared under the Auspices of the Council on Pharmacy and Chemistry of the American Medical Association. Pp. 528. American Medical Association, Chicago, Illinois, 1935.

Twenty-four contributors, mostly outstanding authorities, have contributed a valuable review of recent accomplishments in the field of endocrinology. Most of the readers of this Journal will have already read this material as it appeared serially in the Journal of the American Medical Association but will welcome it in book form. The individual articles—31 in number—are generally based upon extensive study of the literature and good critical judgment. The work presupposes a fairly adequate knowledge of conventional endocrinology, hence would offer difficulty for beginners though most of the authors have given some attention to orienting the reader before getting into the complexities of the subject matter. Each article is accompanied by a well selected bibliography. The typography is excellent and the book is well indexed.

The Adrenals. Grollman, Arthur. Pp. 410, The Williams and Wilkins Co., Baltimore, 1936.

The author has written a useful book. It is readable, and in general satisfactorily inclusive of the significant information now available on the adrenal glands. The historical introduction is especially satisfactory. The work is divided into 14 chapters including anatomical considerations, the physiology and pharmacology of the medullary secretion, the physiology of the cortex and a final section on clinical diseases in which adrenal etiology is important. Particularly interesting is the discussion of the 'androgenic zone' of the cortex which is regarded as an independent physiological entity that plays a special role in the adreno-genital syndrome. A well chosen working bibliography of 704 items concludes the book.

The outstanding defect is the cursory treatment of the evidence bearing on the adaptive significance of the adrenal medulla. Most students in this field will disagree with this conclusion that the function of this structure is essentially unknown. The tacit assumption, too, is made that all of the secretory potentialities of the adrenal cortex are represented in the extract with which the author and his collaborators have obtained experimental familiarity, and in consequence various dubious conclusions are reached. In various instances he has dismissed the work of other inves-

tigators as 'disproven' because the results obtained with their extracts have not been concordant with those he has obtained. Two simple grammatical errors somewhat mar the diction. In several instances 'shall' is used to express third person futurity and 'hypotheticate' for postulate.

Altogether, however, the book will be a welcome addition to the libraries of working endocrinologists.

Time of Ovulation in Women. A Study of the Fertile Period in the Menstrual Cycle. Hartman, Carl G. Pp. 226. Williams and Wilkins Co., Baltimore, 1936.

This book should prove of considerable help in clarifying the situation as regards the sterile period in women. The author presents in a lucid and scientific manner the evidence for and against the theory that the normal woman has cycles of relative sterility and fertility.

The first seven chapters are concerned with a discussion of the anatomy and physiology of the male and female reproductive systems and of the process of ovulation and fertilization. The question of sexual cycles and of biological rhythms in various species of animals is then considered and it is pointed out that the menstrual cycle of women is seldom if ever perfectly regular but varies around a mean of 28-29 days, and that more than half of the women studied have a variability of 11 days or over.

The rest of the book takes up the various methods of determining the time of ovulation. The unreliability of most of the data based on statements of individuals as to time of coitus and occurrence of pregnancy is pointed out.

The evidence presented by Hartman from the study of the time of ovulation and conception in the case of monkeys is both comprehensive and conclusive. It proves beyond question that in the monkey the period of ovulation gives a typical Gaussian distribution such as would be expected in any biological process. He states, "According to present figures she"—the rhesus monkey—"has an absolute sterile period from the twenty-first day on through the seventh day of the succeeding cycle."

The last chapter gives some practical considerations for the clinical application of the 'safe period.' Hartman believes that "most women would remain sterile by abstaining from sexual intercourse between the seventh and the twenty-first nights after the beginning of bleeding." He ends with a plea that if a sufficient number of intelligent women who utilize the method would keep exact records of their sex life, the accumulated data would be extremely valuable.

The book is well written and contains but few typographical errors. On page 118 the statement "no unruptured follicle was found later than eleven days and none earlier than sixteen days prior to the next menstruation" should be changed by replacing the word "none" by "no corpus luteum."

The book is recommended to the general practitioner as a guide for his instruction of women seeking information on this important subject.

Insulin: Its Production, Purification and Physiological Action. Hill, Douglas W., and Frederick O. Howitt, Pp. 219. Hutchinson & Co., Ltd. London, 1936.

This book represents an excellent summary of the extensive clinical and physiological work which has been done on insulin. The authors are to be congratulated upon having produced a most extensive compilation. There is an early chapter upon the preliminary attempts to isolate insulin. This is worthy of study in itself as a record on the one hand of the errors, the preconceived ideas, and the last-hour failures in perseverance which stand in the way of discovery and on the other hand

of the degree to which scientific effort is now interrelated, progress in one field permitting forward steps in a score of seemingly distantly related enterprises. The preparation and purification of insulin is dealt with at length. The literature on insulin substitutes is also examined and the lines of further advance in this direction are described. The work upon the physiological properties of the hormone is also exhaustively reported. It seems probable that the more recent work of Sakel, Pötzl, and Berze upon the effects of large quantities of insulin in non-diabetic subjects will necessitate a later revision of our concepts of hypoglycemia. The various theories of the mode of action of insulin are gone into in detail, and there is a chapter on the standardization of insulin preparations. The authors do not touch upon the clinical uses. The book is one to be recommended.

Outposts of Science. Journey to the Workshops of Our Leading Men of Research. Jaffe, Bernard. Pp. 547. Simon and Schuster, New York, 1935.

This book should prove a godsend to anyone who has occasion to prepare a popular lecture on the subject of endocrinology. In a chapter of some 60 pages the author has brought together a remarkable amount of picturesque information regarding the hormones. While the style is journalistic the selection of material and the distribution of emphasis display a fidelity to the spirit of science that one seldom finds in a work of this sort. True it is that a considerable number of minor slips from meticulous accuracy have crept in but these are of minor importance and in no significant way affect the larger truth that is told.

In addition to the chapter that is of special interest to endocrinologists there are 12 others dealing individually with such subjects as genetics, anthropology, physical disease, vitamins, radiation, astrophysics and weather. The book is illustrated with an occasional text figure and several excellent photographs of workers in the various fields. A well-selected bibliography serves to direct attention to a variety of the more readable type of books in the various fields of science.

It may confidently be predicted that few readers who consult the book for endocrine material will be satisfied until they have read it from cover to cover. They will have been conducted from chromosomes to the galaxies of outer space. The ability of the author to find his way about in such a wide variety of technical fields and to present his garnerings in so fascinating and reliable a way is genuinely remarkable. The book deserves the enthusiastic reception that it will no doubt receive.

Hormone und innere sekretion. Laquer, Fritz. 2nd Edition, Pp. 368. Theodor Steinkopff, Dresden and Leipzig, 1934.

The book forms volume 19 of the "Wissenschaftliche Forschungsberichte Naturwissenschaftliche Reihe" edited by Raphael Ed. Liesegang. It is written by the endocrinologist at the University of Frankfurt. The book is unusual in that it covers every endocrine gland and internal secretion known up to the time of its publication in 1934.

The work comprises an extensive review of the literature on endocrine glands and their secretions. A thousand or more references, many of them in a group, are quoted on each gland. Every phase of endocrinology is treated, including the anatomical, chemical, physiological, clinical and assay aspects of the subject. Little is said in the way of discussion or interpretation of the references cited. The book will be found especially helpful to investigators in covering the vast literature on the various subjects.

ADVANCE ABSTRACTS

Delayed and incomplete union of the epiphyses of the long bones. Beard, E. E. To appear in this Journal.

A case is presented of delayed and incomplete union of the epiphyses of the long bones in a eunuchoid patient 44 years old. Clinical and laboratory findings suggest that this retardation may be due to hypopituitarism with deficiency of sex hormone plus deficiency of growth principles.

Evaluation of hormone therapy for undescended testes in man. Cramer, A. J., Jr. To appear in this Journal.

An attempt has been made to evaluate the use of hormone therapy for the correction of human cryptorchidism. A summary of the published case reports to date, including 20 cases presented herewith, makes a total of 81 cases in the literature. Analysis of the results show that a complete descent of the testes was obtained in 71.6% and a partial result in 16%, making a total of 87.6% that were benefited by this method of therapy. The evidence is sufficient to consider hormone treatment a valuable method of therapy for undescended testes. When surgical correction is indicated, the results may be enhanced by the use of hormone therapy as an adjunct.

Blood chemistry of surviving parathyroidectomized dogs. Evans, E. I., S. Szurek and R. Kern. To appear in this Journal.

A low serum Ca and high serum inorganic P, which according to some workers should precipitate tetany in the parathyroidectomized dog, did not precipitate tetany in parathyroidectomized dogs in latent survival. Serum Ca and inorganic P can remain at tetany levels for at least 9 months in parathyroidectomized dogs without returning to normal. There were no significant changes in Na, K, Mg or chlorides during the survival period after parathyroidectomy.

Report of 1600 Aschheim-Zondek tests (Friedman modification). Feresten, M. To appear in this Journal.

A simplified procedure for the Friedman modification of the Aschheim-Zondek test is described which requires: *a*) the use of ordinary mature, domestic, female rabbits, weighing 5 to 7 lb. or more, which have been isolated in individual cages for 31 days; *b*) a single intravenous injection of 25 cc. of filtered morning urine; *c*) an interval of 48 hours for the interpretation of the ovarian reactions; *d*) the presence of large bulging corpora hemorrhagica for a positive diagnosis. The results of the 1600 tests performed for the early diagnosis of pregnancy were positive in 659 and negative in 941 instances. There were 13 false negative reports, 6 of which were from patients less than a week overdue. There were 2 false positive reports, which in retrospect appear to have been errors of interpretation. The total percentage of error was .94%. Seven cases of tubal pregnancy, with viable chorionic villi, had positive tests. Experimentally, 28 gravid rabbits were injected with urines to be tested for pregnancy. In each case the diagnosis proved correct as checked with the results of nongravid rabbits. In 1 case the test for pregnancy remained positive for 3 days, and in another for 6 days after the removal of the products of conception by curettage.

The site of formation of the posterior lobe hormones. Fisher, C. To appear in this Journal.

Four atrophic posterior lobes of cats with diabetes insipidus were assayed for their melanophore-expanding activity on the live frog. The results indicate that the pars intermedia of these glands was physiologically active as well as histologically intact. The conclusion is therefore drawn that the absence of pressor, antidiuretic and oxytocic activities in glands of the same type as those used in this study is correlated with the degeneration of the pars nervosa and that the latter must play a rôle in the elaboration of these components. The results are discussed with reference to the various theories of posterior lobe hormone formation.

Transplantation of adrenal tissue in Addison's disease. Goldzieher, M. A., H. Koster and S. B. Barishaw. To appear in this Journal.

A case of Addison's disease is reported whose condition resulted from atrophy of the adrenal glands. Post mortem studies showed complete absence of adrenal cortical tissue. This patient was kept alive by administration of salt and cortical extracts for a period of over 2

years. Interrenin (Goldzieher) seemed to give patient the best relief. Adrenal tissue obtained from a case of hypercortical syndrome was transplanted into the rectus muscle. The patient survived the operation for a period of 9 months and appeared to be restored to comparative good health. Autopsy revealed survival of the transplanted cortical tissue in a morphologically adequate state of preservation. The technic and chances of cortical tissue transplantation in Addison's disease are discussed. The use of a donor of the same blood group and stimulation of the graft by injections of the pituitary corticotropic principle are suggested.

Effects on spermatogenesis of a follicle-stimulating extract obtained from menopausal or castrate urines. Huberman, J., H. H. Israeloff and B. Hymowitz. To appear in this Journal.

A follicle-stimulating extract derived from castrate or menopausal urine has been used on 10 male adults suffering from sterility apparently of endocrine origin. In 9 cases the administration of this extract was followed by an increase in the number and motility of the spermatozoa. In no case was the improvement sufficient to render the patient fertile during the period of observation reported. The average dosage of this extract was 50 R.U. given intramuscularly, twice weekly. The total amount administered varied from 300 to 2000 R.U. In no case was the administration of the extract followed by any deleterious effects.

The effect on serum calcium and inorganic phosphate of fractions obtained from crude ovarian extracts. Huey, H. L., and H. W. Marlow. To appear in this Journal.

A study of the effects on serum Ca and inorganic P of the various fractions obtained during the purification of an ovarian extract was made. No fraction or combination of all fractions, including the purified extract, caused any significant or consistent changes in either the serum Ca or the inorganic P.

Excretion of gonadotropic substance in polycythemia vera. Israel, S. L., and T. H. Mendell. To appear in this Journal.

An attempt was made to evaluate the currently-discussed relationship of polycythemia vera to the hypophysis by determining the urinary excretion of the gonadotropic hormone. The precipitation method of Zondek was employed in a study of 6 patients with polycythemia vera. No significant data were uncovered by the investigation, inasmuch as none of the 6 patients showed a demonstrable quantity of the hormone in the urine. The absence of the gonadotropic principle militates against the presence of hypophyseal hyperfunction in this disease.

The quantitative determination of the gonadotropic material of urine of women after castration and the menopause and of normal men. Katzman, P. A. To appear in this Journal.

A comparison was made of the yields of gonadotropic material obtained from the urine of women after castration and the menopause and of normal men, by precipitation with alcohol, tungstic and tannic acids and adsorption on benzoic acid. For the most part, tungstic acid, tannic acid and precipitation with alcohol were equally effective in concentrating the active material of the urine of women after castration or the menopause. The benzoic acid method, however, gave low yields, especially, when the criterion of activity was an increase in weight of the ovaries of the test animals. The activities of the extracts obtained from the urine of normal men by means of tungstic, tannic and benzoic acids were comparable when the toxicity was not excessive. Since these extracts, in the amounts injected, did not produce an increase in the weight of the ovaries of the test animals, the criterion of activity was based on vaginal opening with cornification.

The effects of chronic implantation of rats with pituitaries of the same species. Katzman, P. A., N. J. Wade and E. A. Doisy. To appear in this Journal.

Starting at about the age of puberty, 10 female rats received chronic implantation of anterior lobes of the same species. In nearly all instances the ovaries remained enlarged and in no instance were they sub-normal in weight even after 7 to 9 months of such treatment. The plasma of these animals did not inhibit the gonadotropic effect of implants of rats' pituitaries in immature females. On the contrary, an appreciable augmentation usually occurred. Furthermore, the thyrotropic effect of such implants on the immature guinea pig was not inhibited by the simultaneous administration of this plasma. Therefore, no evidence was obtained for the production of gonadotropic or thyrotropic inhibitory substances in the rats receiving the chronic treatment.

Excretion of male hormones. Kochakian, C. D. To appear in this Journal.

A study of the urinary excretion of male hormones by the capon-comb method of assay was made. The excretion of male hormone by 12 young men 22-29 years of age was apparently not affected by season and was 6 times as great as that excreted by 5 old men 50-76 years of age. Castrated dogs were found to excrete small amounts of male hormone. Male hormone urinary extracts and synthetic androstendione, injected into a castrated man and into 3 castrated dogs as well as into 2 rabbits with tumors of the testicle, could be recovered in the urine only to the extent of 2-6%.

The effect of sex hormones on blood-calcium and inorganic blood-phosphate levels. Marlow, H. W., and F. C. Koch. To appear in this Journal.

The normal blood Ca in fowl fluctuates from 6.1 to 26.7; in rats from 4.7 to 11.1; and in rabbits from 9.1 to 16.0 mg.%. Frequent daily bleedings do not appear to be responsible for consistent changes in the level. A non-crystalline purified estrogenic product prepared from pregnancy urine did not produce a significant and consistent effect on the blood-Ca level in fowl, rats and rabbits. A non-crystalline purified estrogenic preparation from hog ovaries yielded the same results. When gonadectomized rats were studied, the results suggested a slightly lower blood-Ca level than normal and a tendency to a rise after the injection of ovarian estrogenic preparation. A male-hormone concentrate prepared from bull testis-tissue also produced no change in the blood-Ca level in fowl.

The Friedman test and pituitary tumors. McCullagh, E. P., and W. K. Cuyler. To appear in this Journal.

Fifteen cases of pituitary tumor are presented. The diagnoses were verified at operation or autopsy in 8 instances, and the clinical findings were so definite in the others that there was little doubt regarding the diagnosis. The Friedman test gave positive findings in 8 of these cases. When the Friedman reaction is positive, radiation therapy to the pituitary gland may be followed by marked diminution in the excretion of prolan as judged by this test. In 2 instances, this was accompanied by a diminution in the excretion of testicular hormone.

Some effects of synthetically prepared male hormone (androsterone) in the rat. Moore, C. R., and Dorothy Price. To appear in this Journal.

Synthetically prepared androsterone (Ruzicka) injected into castrated male rats prevents the development of castration changes in seminal vesicles and prostate glands at any age and, in proper doses, results in precocious secretory activity of the seminal vesicles. It will maintain normal growth rates of these organs. Injected months after prepuberal or postpuberal castration it restores normal function in these glands. Androsterone in proper doses produces a normal prostate/seminal-vesicle ratio in castrates and by varying the dose this ratio can be varied at will; there is no preferential prostate stimulation when maintainance doses are employed but prostate thresholds are lower than seminal vesicle thresholds. Approximately 3 mg. daily is required to maintain normal seminal vesicle growth in sexually mature males. Androsterone treatment in normal young males reduces testis weight to 12 to 50% of that of untreated littermate controls; testicular injury is evident. Such harmful effects are not apparent in testes of mature adults after 6 mg. daily injections. Gonadotropic potency of pituitaries is abolished in young males treated with androsterone and is reduced in mature adults. Testis injury is believed to be an indirect result from pituitary suppression rather than from a direct effect upon the testis. Small doses failed to indicate any degree of testicular stimulation.

Increased calcium appetite of parathyroidectomized rats. Richter, C. P. and J. F. Eckert. To appear in this Journal.

Appetite for Ca was definitely increased by parathyroidectomy in 17 of 18 rats. The average daily intake of a 2.4% solution of calcium lactate for the 18 animals was 3.9 times as high after parathyroidectomy as before. Replacement therapy with parathyroid implants in 5 animals to the anterior chamber of the eye caused the Ca appetite to return to normal. The Ca needs of 18 normal rats determined by the appetite method averaged 0.056 gm. per day with a maximum of 0.075 gm. which is somewhat lower than the amount, 0.124 gm., calculated empirically by McCollum to be necessary for normal growth. Further evidence is thus obtained showing that appetite is significant in studies of deficiencies created by glandular disturbances or extirpation.

Observations on "prediabetes." Rony, H. R. To appear in this journal.

Twenty cases of 'prediabetes' in obese persons were observed in the clinic for 1 to 9 years. None of them have developed diabetes. In the majority of the cases marked increase in glucose tolerance was found at the end of the observation period; permanent decrease did not occur in any case. The changes in glucose tolerance were significantly but not invariably related to the changes in body weight. There is no direct evidence that low sugar tolerance in obesity is a precursor to diabetes. Obese persons with low sugar tolerance respond to low carbohydrate diet or fasting with immediate increase of sugar tolerance; high carbohydrate diet promptly depresses the sugar tolerance. This is the opposite of what is known to occur in normal and underweight persons. It appears that this behaviour of the obese is due to the capacity of the fat tissues to absorb large amounts of glucose from the blood when glucose is ingested after a period of undernutrition.

Experimental studies of the anterior pituitary. The replacement capacity and non-cyclic behavior of homoplastic anterior pituitary grafts. Schweizer, M., H. A. Charipper and H. O. Haterius. To appear in this Journal.

Intra-ocular implants attached to the pupillary margin of the iris and extra-ocular implants in the lateral subjunctival tissues become dominantly basophilic and retain their gonadtropic capacity in completely hypophysectomized guinea pigs. The ovaries become progressively more follicular until, after approximately 2 months, a condition of constant estrus supervenes. This condition is characterized by a continual estrus vaginal smear, by a markedly hypertrophied uterus and by well proliferated mammary glands. The ovarian effect of such implants is exclusively a follicle-stimulating one; the ovaries contain no well defined luteal bodies and the endometrial pattern, moreover, is typically that brought about by estrin influence. The complete absence of luteinizing hormone is further attested by the absence of fully mature follicles and of ovulation. On the basis of these observations, the conclusions are advanced that the hypophyseal grafts are functional in maintaining the ovaries in the follicular phase and that the guinea pig pituitary when transplanted to a site removed from its normal anatomical position loses its cyclic character. This cyclic failure, in all probability, is due primarily to the severance and non-regeneration of its normal neural and vascular connections.

The treatment of undescended testes with anterior pituitary-like substance. Thompson, W. O., A. D. Bevan, N. J. Heckel, E. R. McCarthy and P. K. Thompson. To appear in this Journal.

The effect of treatment with APL substance from pregnancy urine was observed in 21 undescended testes in 18 boys from 1.5 to 17 years of age. In 8 instances the testes were intra-abdominal and in 13 inguinal. The dose of APL substance varied but commonly was about 200 R.U. 3 times a week for an average of 5 months. Descent occurred in 4 patients (19%). In all 4 the testis was in the inguinal canal before treatment and in 2 could be pushed to the upper end of the scrotum. Descent occurred within 1 month in all 4. In 1 of these 4 patients the testis returned to the inguinal canal when treatment was stopped. In 7 other patients, treated surgically after prolonged administration of APL substance, anatomical factors making descent difficult or impossible were present. However, preoperative treatment with this material caused definite stimulation of genital growth and thus seemed to make surgical procedures less difficult.

Further studies on the action of parathyroid extract in the dog following total and partial ablation of the kidneys. Tweedy, W. R., R. D. Templeton and F. A. McJunkin. To appear in this Journal.

The serum Ca values and the microscopic observations at necropsy indicate that parathyroid extract is ineffective in the bilaterally nephrectomized dog, which has been injected, intramuscularly with calcium gluconate. After bilateral ligation of the ureters the reaction of the dog to parathyroid extract is irregular and slightly suggestive of hormone effect. The unilaterally nephrectomized dog reacts to parathyroid extract in a manner comparable to the normal dog.

The effect of anterior pituitary-like hormone on the blood picture in rabbits. Wilson, D. To appear in this Journal.

APL, 193 injections of 100 R.U. each, was injected into the marginal veins of 11 virgin female rabbits weighing between 4 and 8 pounds. Baseline counts had previously been made over a period of 1 to 1½ months. Total differential and reticulocyte counts were made before each injection and at varying periods following the injection. A marked leucocytosis was found

to occur within 5-8 hours. Lymphocytes were correspondingly depressed. The red cell count remained unaltered. A return to the normal baseline occurred in 5-6 days. When the injections were repeated every other day over a period of several weeks less and less leucocytic response was elicited by a single injection until finally no response was secured. It would appear from this that a certain tolerance was established to frequent injections. The initial leucocytic response could however be elicited again if the injections were interrupted for 2 weeks.

The importance of corticoadrenal regulation of potassium metabolism. Zwemer, R. L., and R. Truszkowski. To appear in this Journal.

The importance of the adrenal cortex in regulating K metabolism is discussed in relation to the following observations. There are definite changes in the blood and muscle K of adrenalectomized cats, which can be correlated with the observed symptoms. Furthermore, the various manifestations of the syndrome of adrenal insufficiency were reproduced in normal mice, rats, guinea pigs and cats by intraperitoneal injection of solutions of K salts in amounts which will raise and maintain the plasma K at levels found in adrenalectomized animals during similar phases of the syndrome. Lethal potassium doses for the above species are also given. Adrenalectomized animals were found to be unable to adequately deal with certain definite amounts of K, although much larger amounts were easily disposed of by normal animals. Potassium tolerance as a quantitative measure of adrenal insufficiency should be judged by frequent determinations of the blood-K level after K administration. Injections of adrenal cortex extract (Zwemer) protect normal mice and guinea pigs, to some extent, from otherwise fatal amounts of K administered intraperitoneally. Corticoadrenal extract also lowers the blood K of normal cats.

ADRENALS

Chemical changes in the blood in Addison's disease. Allot, E. N., Lancet **230:** 1406. 1936.

Eight cases of Addison's disease are presented with detailed chemical studies. The characteristic blood changes in experimental suprarrenal insufficiency consist of a fall in sodium and chlorine content of the serum, a rise in the potassium and magnesium, a retention of nitrogen (high blood urea and non-protein nitrogen) and increased concentration of the blood (high oxygen capacity and haematocrit values and high serum protein). Of the eight cases described in this paper all showed to greater or less extent changes on first observation. Two of the patients went into crisis; in crisis there is frequently a marked rise in non-protein nitrogen. The chemical findings suggest that cortical hormone will bring the potassium and urea down to normal, but has little effect on the sodium and chlorine. If the potassium and urea however, begin to rise, while the patient is being treated with salt it is advisable to add cortical hormone. In these cases there was not always present a correlation between the alteration in the patient's clinical condition and the level of sodium and chlorine in the serum.—L. B. S.

Relation of the adrenal cortex to reproduction and lactation. Britton, S. W., and R. F. Kline, Am. J. Physiol. **115:** 627. 1936.

Of 64 adrenalectomized female rats mated with normal males 5 became pregnant, all bearing normal litters, but in only 2 was lactation normal. All 4 possessed accessory adrenals. Thirty-five of 64 normal female rats mated with adrenalectomized males became pregnant and gave birth to normal litters. In a normal control series 44 pregnancies occurred. Removal of 1 adrenal in pregnancy caused resorption of fetuses in 3 of 8 experiments. Complete adrenalectomy brought about abortion or resorption of the fetuses. Traumatizing operations of greater severity commonly do not effect pregnancy in the rat. Cortical extract enabled adrenalectomized rats (5) to bear litters and to lactate. Double or single adrenalectomy terminated pregnancy in the 20 cats.—F. A. H.

Hyperchromaffinism. Chamberlain, D., Brit. M. J. **1:** 1251. 1936.

The author reports a case of chronic hypertension in which there were periodic attacks of convulsions and coma associated with a blood pressure of 218/140. The patient was operated upon in the belief that the disorder was due to hyperchromaffinism. One adrenal was removed at operation, although both glands appeared grossly normal. The pathological report did not confirm the clinical impression but the patient improved to the extent of having only 2 attacks of headache and vomiting during the first 4 months succeeding operation. The blood pressure remained at 216/144. The author suggests that the syndrome was due to an abnormal secretion of the adrenal medulla, and that the hypertension persisted after operation because of pathological changes in the heart and blood vessels.—H. B. Friedgood.

Lactation in adrenalectomized rats. Gaunt, R., and C. E. Tobin, Am. J. Physiol. **115:** 588. 1936.

Adrenalectomized rats treated with cortical adrenal extract (Swingle and Pfiffner method) raised their litters in 4 of 10 cases; the growth of the surviving young was sub-normal when the dose was just adequate for the mother. Similar results were obtained with adrenalectomized rats given salt treatment only. Salt treatment plus adequate cortin resulted in lactation that approached normal. When the amount of cortical extract was double that adequate for the mother lactation was normal. Sub-total adrenalectomy did not influence lactation. Lactation was produced in only half of a series of follutein-treated females, ovariectomized 5 days after adrenalectomy. Prolactin had no influence on the deficient lactation due to adrenalectomy. Anterior pituitary extract (growth hormone) inhibited lactation in adrenalectomized rats maintained on a sub-minimal dose of cortical extract. The results are interpreted as offering no support to the hypothesis that the adrenal cortex produces a lactation hormone.—F. A. H.

Hirsutism, hypertension and obesity associated with carcinoma of the adrenal cortex. Indeterminate pituitary adenoma and selective changes in the beta cells (basophils) of the hypophysis. Graef, I., J. J. Bunim and A. Rottino, Arch. Int. Med. **57:** 1085. 1936.

This paper is a review of literature on the subject with details of an illustrative case. The case is reported of a 19 year old girl who presented hirsutism, hypertension, obesity and striae atrophicae in life and at necropsy was observed to have a metastasizing carcinoma of the adrenal cortex and an indeterminate military adenoma of the anterior lobe of the pituitary gland. Selective degenerative changes were noted in the nuclei of the beta cells of the pars anterior of the hypophysis. Although data are not conclusive, evidence is given which tends to show that the pituitary adenoma is not merely a coincidental finding. Attention is drawn to the co-existence of clinical manifestations or pathologic evidence of changes in the pituitary gland in similar cases of metastasizing adrenal neoplasm recorded in the literature. Marked overexcretion of estrogenic substance in the urine was noted during life, and this is discussed in relation to the atresia and atrophy of the ovaries and endometrium.—I. B.

Inversion of the action of adrenalin on blood sugar by yohimbin (Inversión de los efectos de la adrenalina sobre la glicemia en el perro yohimbinizado). Gutiérrez Noriega, C., and V. Manrique. Actual. Med. Peruana. **1:** 519. 1936.

Dogs received 2-3 mg. yohimbin per kg. and then adrenalin 0.02 mg. intravenously; the blood sugar was determined before the injection of adrenalin and when the blood-pressure was at its lowest. The blood sugar usually rose 20-40 mg. % above the initial level. A second injection in most cases, but not in all, produced hypoglycemia.—J. T. L.

Formation of an epinephrin-like substance in autolyzing adrenal glands. Larrain, A. R., R. G. Roberts and M. M. Kunde, Am. J. Physiol. **115:** 662. 1936.

Autolysis of crushed, whole adrenal glands gave rise to a powerful pressor substance obtained by dialysis. This gave all the ordinary chemical tests for adrenalin, but differed in that it was not precipitated by concentrated ammonium hydroxide. It did not give a biuret reaction; was not destroyed by boiling for 1 min.; was adsorbed by animal charcoal and aluminum hydroxide and did not lose its physiological effect if exposed to air at room temperature for 30 days. Glacial acetic acid did not destroy it. Inhibiting autolysis of the crushed adrenal glands by the addition of potassium cyanide prevented its formation. The formed pressor substance could be removed from the crushed glands by repeated washing. Further autolysis, however, resulted in the formation of more pressor substance, which continued to form until practically complete disintegration of the gland substance had occurred.—F. A. H.

Observations on the pathological changes in suprarenalectomized dogs, with particular reference to the anterior lobe of the hypophysis. Nicholson, W. M., Bull. Johns Hopkins Hosp. **58:** 405. 1936.

Autopsy of 25 adrenalectomized dogs revealed no characteristic pathological changes. No histological changes were observed in the anterior lobe of the hypophysis. In 3 cases of Addison's disease due to cortical atrophy a reduction in the basophil cells of the hypophysis was evident. No changes occurred in 4 cases due to tuberculosis.—A. G.

On the constituents of the adrenal cortex (Über die Bestandteile der Nebennierenrinde, II, III, & IV). Reichstein, T., Helv. Chim. Acta **19:** 223; 401; 402. 1936.

One of the crystalline substances isolated by the author from potent adrenal-cortex extracts

(substance G, an unsaturated diketone probably $C_{19}H_{24}O_2$) is about one-fifth as active as androsterone in causing growth of the comb of the capon, and is therefore named andrenosterone. The assay was performed by Dessau's method of painting an oil solution of the substance directly on the comb. The discovery of a substance with male-hormone properties in cortical extracts is important in connection with the relation between cortical tumors and virilism. The substance is not estrogenic, and is not identical with any known male hormone. Three of the other substances isolated (A, B, and C) all yield the same diketone ($C_{19}H_{26}O_2$, m. p. 178°) when oxidized with chromic acid; this diketone has one-third of the potency of androsterone. Alkaline saponification of the petrol-ether-soluble fraction of the extracts yielded a substance $C_4H_{10}O_2S$, which has been identified with synethetic di-hydroxyethyl-sulfoxide $(HOCH_2 \cdot CH_2)_2SO$. No compounds of this type have hitherto been obtained from animal tissues. It is not stated whether any of the substances described affect the survival of adrenalectomized animals.—D. L. T.

The alarm reaction. Selye, H., Canad. M. A. J. **34:** 706. 1936.

Serious non-specific injury produced in rats by exposure to cold, surgical shock, or sublethal doses of various drugs, evokes a typical syndrome, the first stage of which ('alarm reaction') includes edema formation, appearance of acute ulcers in the digestive tract, fall of body temperature, and rapid involution of the thymus and lymph glands. These changes are ascribed to liberation of histamine or some similar substance into the circulation. Adrenalectomy sensitizes the animals to all stimuli causing an alarm reaction, but completely prevents the involution of the thymus.—D. L. T.

Carbohydrate and electrolyte changes in the opossum and marmot following adrenalectomy. Silvette, H., and S. W. Britton, Am. J. Physiol. **115:** 618, 1936.

Following double adrenalectomy, serum sodium and chloride increased 8% and 10%, respectively, in the opossum (11 cases) and about 4% each in the marmot (7 cases). Muscle sodium and chloride were increased while muscle water was decreased in the opossum. Double adrenalectomy reduced the excretion of sodium and chloride by the kidney in the opossum (5 cases). Muscle water was slightly decreased in the marmot. These findings are the reverse of those obtained from common laboratory animals. However the blood glucose and liver glycogen are considerably decreased and the muscle glycogen of the opossums and marmot are notably decreased as in other animals after adrenalectomy. It is suggested that the vital hormone of the adrenal cortex affects sodium chloride balance only indirectly while the regulation of carbohydrate metabolism is a direct effect.—F. A. H.

The effect of accelerator nerve stimulation and of adrenalin on recovery from ventricular fibrillation in the cat. Smith, D. C., and A. G. Mulder, Am. J. Physiol. **115:** 507. 1936.

In most cases of 12 cats under dial anaesthesia spontaneous recovery from ventricular fibrillation following faradization of the ventricles occurred. The duration of fibrillation varied directly with the weight of the cat (size of the heart). Stimulation of the accelerator nerves during ventricular fibrillation shortened the duration of the fibrillation. While the heart was under the influence of adrenalin (0.1-0.5 cc. of 1:1000) recovery from fibrillation of the ventricles was practically instantaneous.—A. J. Derbyshire.

Vitamin C and the adrenal cortical hormone. Svirbely, J. L., and E. C. Kendall, Am. J. Physiol. **116:** 187. 1936.

Two adrenalectomized dogs maintained on a diet free of vitamin C failed to develop scurvy. There was ordinarily no change in nitrogen metabolism when cortin was deficient. Using 3 guinea pigs on each point the authors found no appreciable effect of cortin in delaying the onset of scurvy.—F. A. H.

So-called atrophy of the adrenal cortex with intranuclear inclusions. Weiner, H. A., Am. J. Path. **12:** 411. 1936.

A case of 'atrophy' of the adrenal glands in a 53 year old Jewish woman is described. The apparently sudden onset after a slight trauma and the rapid clinical course are noteworthy. Intranuclear inclusion bodies were found in the cortical cells of the adrenal glands which were much reduced in size and lacked the normal histological structure. The thyroid gland was made up of small follicles with abnormally-staining colloid. It showed no signs of hyperplasia but there was considerable leucocytic infiltration. Serial sections of the hypophysis failed to reveal any abnormality.—W. J. A.

The distribution of adrenergic vasodilators in the rat. Wyman, L. C., and Caroline Tum Suden, Am. J. Physiol. **116:** 182. 1936.

The differential effects of adrenalin chloride on the blood pressure were studied in rats under urethane anesthesia. Reduction in the splanchnic circulation reduced the pressor response to 0.1 cc. of 10^{-6} adrenalin about one-half; to 0.1 cc. of 10^{-5} adrenalin, only slightly or not at all. Reduction in the peripheral circulation increased the pressor responses to small amounts of adrenalin. Depressor responses to small doses of adrenalin in rats with the suprarenal medulla eliminated were somewhat decreased after splanchnic reduction and much decreased after peripheral reduction. Depressor responses to adrenalin revealed in normal rats after treatment with ergotamine were unaltered by either type of circulatory reduction. It is concluded that in the rat, as in the cat, adrenergic vasoconstrictors are more abundantly distributed to the splanchnic area as compared with the peripheral area but that the rat, unlike the cat, has a significant distribution of adrenergic vasodilators to both regions. The biological significance of this apparent interspecific difference is discussed.—F. A. H.

Effects of prepuberal gonadectomy on the adrenal gland of the guinea pig. Zalesky, M., Anat. Rec. **65:** 467. 1936.

Two varieties of liposomes are distinguished in the fasciculate zone of the guinea pig adrenal: The microliposome, 0.4 to 2.5 μ in diameter, and the macroliposome, 3.5 to 20 μ in diameter. The number of macroliposomes is conspicuously greater in the adrenal of the adult female as compared with that of the adult male. Sex differences in the distribution of the macroliposomes, as well as in the relative width of the cortical zones, are likewise described. These sex differences develop and persist also in prepuberally gonadectomized guinea pigs. Prepuberal gonadectomy induces no significant permanent hypertrophy or atrophy in the guinea pig adrenal. It does, however, cause a lipoid increase in the adrenal cortex. The lipin bodies most frequently and most conspicuously involved are the macroliposomes. These effects are particularly pronounced in the female, and extreme cases of macroliposomal increase, accompanied by intensive cell destruction in the fasciculata and extensive focal necroses in the reticularis, are encountered among adrenals of spayed females.—Author's Abst., Wistar Bib. Service.

ENDOCRINE GENERAL

Is a portion of the pancreatic secretory response to a meal due to the absorption of digested food products? Gray, J., M. S. Kim and A. C. Ivy, Am. J. Physiol. **116:** 210. 1936.

The effect on the secretion of pancreatic juice of the intravenous injections of liver extract, Witte's peptone, dextrose and emulsified fats was investigated. None of these substances in concentrations comparable to that absorbed from the intestine produced an appreciable effect. It is concluded that secretin is probably the only humoral agent concerned in the secretory response of the pancreas to a meal.—F. A. Hitchcock.

Lesions in the pancreas and in the anterior hypophysis with fatal acidosis following prolonged intravenous administration of glucose (in dogs). Jacobs, H. R., and A. R. Colwell, Am. J. Physiol. **116:** 194. 1936.

The continuous intravenous injection of 22 normal female dogs with glucose at rates varying from 0.7 to 4.5 gm. per kg. per hour resulted in a mild congestion of all viscera with severe hemorrhage and degenerative changes in the pancreas and anterior hypophysis. Hepatic glycogen increased and alkali reserve decreased. All dogs died of acidosis in from 20 to 168 hours. The accumulation of an acid intermediate product of glucose metabolism is postulated. —F. A. Hitchcock.

Experiments to isolate the antianemic principle of the liver. Laland, P., and A. Klem, Acta med. Scandinav. **88:** 620, 1936.

Fresh hashed liver was extracted with 50% acetone and the resulting solution concentrated. The protid was removed by sulphosalicylic acid and the active protid-free filtrate extracted with phenol. The phenol solution quantitatively removes the antianemic principle, which can be recovered by adding ether and water. The water layer was treated with active charcoal and the adsorbed principle removed from the charcoal by phenol. The material was soluble in ethyl and methyl alcohol and glacial acetic acid and could be precipitated by ether or saturation with ammonium sulphate. By a combination of these methods a fraction was obtained of

which 0.7 mg. gave a good anti-anemic effect. An elementary analysis of the material gave 13.33% N., 53.64% C., 6.85% H. and 0.74% S. The active fraction was completely free from the strongly yellow-green fluorizing liver flavine.—J. M. L.

Changes observed in the parathyroids, thyroid and adrenals following experimental deviation of the bile flow (Des modifications de quelques glandes a secrétion interne: parathyroides, thyroids, surrénales, consécutivement a la dérivation biliaire expérimentale). Leriche, R. and A. Jung, Presse méd. **43:** 1793. 1935.

A deviation of the bile from the bile-duct into the urethra was effected in 17 dogs. As a consequence, the thyroids of the animals showed enlargement of both lobes and an increase of the vesicles, which were filled with colloid—a sign of hypofunction. The parathyroids revealed on examination signs of hyperfunction—hyperplasia, dilated capillaries, absence of lipoid and edema between the cell bundles. The volume of the adrenals was moderately increased; the cortex showed abundance of spongiocytes, the medulla was congested. Reimplatation of the bile duct into the intestine caused the thyroid to return to normal, but parathyroids and adrenals remained in the state of hyperfunction. Two clinical cases of biliary fistula are reported showing changes in the glands similar to those observed experimentally.—A. E. Meyer.

Progress in endocrinology. Anon. Prescriber **30:** 141. 1936.

The May issue is devoted to a readable and informative review of recent work on the various endocrine glands.—R. G. H.

GONADS

Some notes on the isolation of oestrone and equilin from the urine of pregnant mares. Beall, D., and M. Edson, Biochem. J. **30:** 577. 1936.

From the weakly-acidic phenol fraction of a toluene extract of acid-hydrolysed urine, oestrone and equilin were found to be precipitated as mercury-ketone complexes: the equilin-mercury complex is soluble in alcohol.—D. L. T.

Occurrence of glycogen in endometrial hyperplasia and its significance (Das Vorkommen von Glykogen bei der glandulär-cystischen Hyperplasie der Uterusschleimhaut und seine Bedeutung). Breipohl, W., Zentralb. f. Gynäk. **60:** 1481. 1936.

A study of 80 cases showed glycogen absent in 65%, small areas of glycogen in 26%, and extensive glycogen in 9%. It appeared that luteinization had occurred in the latter group. Theoretical considerations suggest that generalized glycogen formation in the endometrium depends on action of the progestin.—E. L. S.

On Δ_1 -androstenedione (Über Δ_1 -androstendion-3, 17). Butenandt, A., and H. Dannenbaum, Ber. d. chem. Gesellsch. **69:** 1158. 1936.

On 6-keto-testosterone and related compounds (Über 6-Oxotestosteron und verwandte Verbindungen). Butenandt, A., and B. Riegel, Ber. d. chem. Gesellsch. **69:** 1163. 1936.

Three new synthetic members of the male hormone series are described. The first is isomeric with the known androstene-dione but has the double bond at C_1 instead of C_4; the others differ from androstene-dione and testosterone, respectively, only in having an extra ketone group introduced at C_6. These 3 compounds seem to have lost male-hormone properties, not affecting the capon comb at doses up to 4 mg., but all 3 of them have acquired estrogenic properties; 4 doses of 500 gamma, subcutaneously in oil, produced full estrus in adult castrate female mice.—D. L. T.

A case of extreme sex-modification in an adult bovine free-martin. Buyse, A., Anat. Rec. **66:** 43. 1936.

In the reproductive tract of an adult free-martin twin with 2 normal males, a highly contorted penis-like structure 26 cm. in length, penetrates the wall of the vestibul and terminates in a glans penis. No scrotum is present, nor is there any trace of either uterus or vagina. As in males, the urethra and paired vasa deferentia open directly into the urino-genital sinus. Lobulated seminal vesicles empty into these ducts proximally. A urethral muscle surrounds the urinogenital sinus at its junction with the urethra as in the male, but no prostate gland is found. Both gonads are of the free-martin type situated subcutaneously in the groin. Seminiferous

tubules, medullary cords, epididymis and a rete penetrating the gonad for two-thirds of its length are striking features. Primordial germ cells are absent. To account for such modification the following possible explanations are offered. 1) Secretion of a high concentration of male hormone by the 2 male co-twins. 2) Retardation of the female embryo due to late fertilization or delayed ovulation and its response to the influence of the male hormone while the external genitalia are still morphologically indifferent.—Author's Abst., Wistar Bib. Service.

Stimulation of the male gonads by female sex hormone (Die Stimulierung der männlichen Geschlechtsdrüse durch weibliches Sexualhormon). Clauberg, C., Zentralbl. f. Gynäk. **60:** 1457. 1936.

Estrogenic hormones have been reported to stimulate and to inhibit the gonadotropic activity of the anterior lobe. Single large doses have been shown to lead to increased gonadotropic effects, sometimes followed by a temporary decrease and then resumption of previous activity level. In this paper results are illustrated from rat experiments in which such doses as 5000 mouse units of commercial follicle hormone were injected into males. There appeared to be testicular hyperemia, enlargement, and microscopic evidence of increased cellular activity. The subjects were more belligerent toward other males and were sexually active, with pregnancy following mating. After treatment followed a period of sexual inactivity and then resumption of activity. Although gonad hormones are not homo-stimulative, they do cause vascular reactions leading to hyperemia, regardless of the sex of animal or of hormone, and that this hyperemia may temporarily modify gonad activity.—E. L. S.

Oestrin treatment of cystic disease of the breast. Dahl-Iverson, E., Lancet **230:** 1294, 1936.

Twenty-two cases of cystic mastopathia were treated with estrin and considerable recovery was obtained in 18. In 2 patients, both between 20-30 years of age, the local and general condition was aggravated, and in 2 cases there was no effect. The author in view of his experience with this condition advises a daily dose of 2000-4000 mouse units by mouth or 10,000-20,000 mouse units once a week given intragluteally. The course of treatment should last 3-6 months. Surgery should be regarded as inadvisable unless estrin proves of no avail.—L. B. S.

The experimental induction of oestrus (sexual receptivity) in the normal and ovariectomized guinea pig. Dempsey, E. M., R. Hertz and W. C. Young, Am. J. Physiol. **116:** 201. 1936.

Sexual receptivity followed in 14% of 21 normal females injected with 1000 I.U. theelin and in 31% of 30 spayed females given distributed injections. The latent period averaged 35.3 hours. The intravenous administration of 0.2 gm. equivalents of sheep luteinizing hormone induced heat and ovulation in 19% of 24 cases in normal animals on the 12th to the 15th day of dioestrum, after a latent period averaging 5.8 hours. Such treatment was ineffective earlier in the cycle. Similar injections of luteinizing hormone into spayed females were ineffective. In the spayed female the combination of estrin and luteinizing hormone did not augment the efficacy of estrin alone; 40 I.U. or more of estrin, followed in 36 to 48 hours by 0.2 I.U. progesterone, induced heat in 24 spayed females, the latent period averaging 4.8 hours. Of 9 normal animals injected with progesterone alone on the 14th or 15th day, 7 came into heat within 5 to 10 hours but did not ovulate. It is believed that progesterone is directly involved in the production of sexual receptivity in the guinea pig. The rise in estrin level toward the end of the cycle conditions the animal for estrus, the appearance of which, however, depends upon the subsequent action of progesterone which is produced by the still unruptured or preovulatory follicle after it has been acted upon by the luteinizing hormone of the hyophysis. —H. O. Haterius.

New substances affecting the seminal vesicles of the castrate mouse (Neue Stoffe mit starker Kirkung auf die Vesikulardrüsen der kastrierten mannlichen Maus). Dirscherl, W., J. Kraus and H. E. Voss, Ztschr. f. physiol. Chem. **241:** 1. 1936.

Catalytic hydrogenation of crystalline or crude estrin from mare's urine leads to the formation of substances which have been partly purified and which possess up to one-fifth of the activity of testosterone in promoting growth of the seminal vesicles of the castrated male mouse, but which have no action upon the comb of the capon even when directly applied thereto, and are thus different from all androgens hitherto known. Less potent preparations of similar substances have been obtained without hydrogenation from wool-fat and Peruvian bark.—D. L. T.

Synthetic oestrogenic agents without the phenanthrene nucleus. Dodds, E. C., and W. Lawson, Nature **137:** 996. 1936.

Hitherto all natural or synthetic estrogenic agents have contained the phenanthrene ring-system, more or less hydrogenated and substituted. A series of new substances possessing similar biological properties but without this ring-system are listed. The simplest members are 4:4′-dihydroxy-diphenyl and 4:4′-dihydroxy-benzophenone, which produce estrus in ovariectomized rats when 100 mg., divided into 6 doses, is injected in oil solution. The most potent of the new substances is 1:2-dihydroxy-1:2-di-alpha-naphthyl-acenaphthene, of which 10 mg. is an adequate total dose, while 100 mg. maintained the rats in continuous estrus for 40 days. In the simpler compounds, the para-position of the hydroxyl groups is of importance for the effect.—D. L. T.

The corpus lutem hormone content of human placenta. (Untersuchungen über den Gehalt der menschlichen Placenta an Corpus-luteum-Hormon.) Ehrhardt, C. and H. Fischer-Wasels. Zentralbl. f. Gynäk. **60:** 787. 1936.

The progestin content of placental tissue is low in the first 3 months, rises to its maximum in the 6th or 8th months, and falls near term. In a few cases of children carried past term the placenta seemed to have unusually high progestin content. These results are held consistent with the Knaus theory of the mechanism initiating parturition. Two cases of habitual abortion and one of amenorrhea were treated with extracts of placenta, extracted to remove estrin. Results are considered satisfactory, but there is no evidence of progestin being contributed directly by the preparations used.—E. L. S.

Effect of oestrogenic hormones on lactation in the cow. Folley, S. J., Nature **137:** 741. 1936.

The injection of 500 mg. oestrone and 50 mg. oestradiol-benzoate in 3 days in a lactating cow decreased the milk yield by 20%, but increased the concentration of phosphatase and of non-fatty solids in the milk; these effects were still evident two weeks after the injections.—D. L. T.

The bitterling test for pregnancy. Gottlieb, R., Canad. M. A. J., **34:** 431. 1936.

The bitterling-ovipositor test for pregnancy, according to Kantor, Bauer and Klowans, was studied; 36 specimens of pregnancy urine all gave positive tests, but about 20% of non-pregnant, immature, or male urines tested also gave positive results.—D. L. T.

Observations of treatment of pruritus (Beiträge zur Pruritusbehandlung). Kaufmann, C., Zentralb. f. Gynäk. **60:** 850. 1936.

Seven patients with severe pruritus about the genitalia were treated with large doses of estrogenic hormone, usually "Oestradiolbenzoat" or "Progynon-B." Relief was very gratifying, both in cases with visible changes in the skin and with kraurosis, and in those with no changes seen. Cases were in spontaneous climacteric, artificial menopause, or with genital hypoplasia. One patient had a severe pruritus generally, and with edema and skin changes about the eye lids. No mention is made of the permanence of results, or of maintenance doses.—E. L. S.

Therapeutic uses of ovarian hormones (Aplicaciones terapéuticas de las hormonas ováricas). Kaufmann, C., Semana méd. **42:** 171. 1936.

The action of follicular and corpus luteum hormones is discussed. The author calculates the range of dosage on the basis of determinations made on castrate women. About 250,000 units of follicle hormone are necessary to produce a proliferation of the endometrium equal to the physiological conditions, and 35-50 Clauberg units of corpus luteum hormone to produce secretion. Oral medication requires about 10 times the parenteral doses. The follicle hormone is generally not effective in primary amenorrhea. Hormonic treatment is indicated in secondary amenorrhea only if the general examination is negative. Only cases of at least 6 months duration should be treated since spontaneous recurrence of menstruation is quite common. The treatment with doses of 50,000 units must be carried on for 3 to 6 or more months. A return of a spontaneous cycle was obtained in 25% of the cases treated. The symptoms of surgical menopause are favorably influenced by doses of 50,000-100,000 units. Ulcerations of vagina and vulva concomitant to amenorrhea yielded satisfactorily to doses of 600,000 or 800,000 units. Severe uterine hemorrhages subsided after treatment with corpus luteum hormone.—A. E. Meyer.

INDEX TO VOLUME 20

ORIGINAL ARTICLES

Acromegaly followed by pituitary calcification, 847
ADAMS, A. E., and E. N. WARD. The effect of hypophysectomy and of phyone injections on the pancreas and liver of the newt, 496
Addison's disease and adrenal atrophy, 383
Adrenal atrophy and Addison's disease, 383
cortex extract, weight changes due to, 565
cortical extract and bacterial toxins, 93
cortical tumor, 567
Adrenal gland, effect of alkaline extract of anterior hypophysis upon, 159
effect of estrogenic substances on, 746
pressor effect of glycerine extract of, 188
Adrenalectomy, survival after, 550
survival after, 556
AGRESS, C. M. See Bodansky, M., 684
ALBRIGHT, F. Studies on ovarian dysfunction III The menopause, 24
ALLEN, E., A. W. DIDDLE, T. H. BURFORD and J. H. ELDER. Analyses of urine of the chimpanzee for estrogenic content during various stages of the menstrual cycle, 546
ALLEN, E. See Burford, T. H., 635
ALLEN, W. M. See Reynolds, S. R. M., 681
Allergic reactions, influence of endocrine preparations on, 171
ALPERS, B. J. See Mazer, C., 753
ANDREW, R. H., and F. FENGER. The isolation from ovarian tissue of a crystalline substance possessing high estrogenic properties, 563
Anterior pituitary extract in treatment of pituitary infantilism, 854
Anterior-pituitary-like hormone of pregnancy urine in sexual underdevelopment, 781
Antidiuretic activity of posterior lobe, effect of interruption of supraoptico-hypophyseal tracts on, 762
Anti-gonadotropic substances, 311
Antuitrin S, effect of, on sexually inactive male ground squirrel, 219
Arrhenoblastoma, case of, 373
AYRES, G. B. See Lee, M., 489

Bacterial toxins and cortico-adrenal extract, 93
BAKER, B. L., and G. E. JOHNSON. The effect of injections of Antuitrin-S on the sexually inactive male ground squirrel, 219
BALDWIN, L. G., and J. A. GAFFORD, JR., Arrhenoblastoma case report, 373
BARBER, A. S. See Watson, E. M., 358
BARR, D. P. See Bulger, H. A., 137
BARR, D. See Orgel, M. N., 839
BATES, R. W. See Riddle, O., 1
BENNETT, R. J., JR. A simple method of hypophysectomy in dog, 860
BERMAN, L. Studies of Paget's disease II. The effect of adreno-cortical extract treatment upon the blood phosphotase in Paget's disease, 226
BLOCH, P. W. Progestin content of blood, 307
Blood iodin level, influence of calcium intake on, 809
Blood, progestin content of, 307
Blood volume, effect of estrogenic substance on, 329
BODANSKY, M., C. M. AGRESS, K. R. CAMPBELL and C. L. HERRMANN. Mortality following bilateral adrenalectomy combined with renal decapsulation, 684
BODANSKY, M., and V. B. DUFF. Age as a factor in the resistance of the albino rat to thyroxine, with further observations on the creatine content of tissues in experimental hyperthyroidism, 541
BODANSKY, M., and V. B. DUFF. The influence of pregnancy on resistance to thyroxine, with data on the creatine content of the maternal and fetal myocardium, 537
BODANSKY, M., and V. B. DUFF. Nitrogen and creatine metabolism in relation to environmental temperature and thyroid function, 822
BOISSEVAIN, C. H., and W. F. DREA. Relation between the occurrence of endemic goiter and the presence of traces of silver and barium in drinking water, 686
BRAM, I. Dating endocrine substances: a plea for fresh products, 866
BRAZIER, M. A. B. The impedance angle and thyroid disease, 621
BULGER, H. A., and D. P. BARR. Metabolic studies of pituitary insufficiency, 137
BURCH, J. C. See Ellison, E. T., 746
BURDICK, H. O. See Whitney, R., 643
BURFORD, T. H., E. ALLEN, and A. W. DIDDLE. Effect of total thyroidectomy upon mature ovariectomized monkeys, 635
experimentally induced menstruation in
BURFORD, T. H. See Allen, E., 546

Cachexia hypophyseopriva, case of, 149
Calcium intake and blood iodin level, 809
Calorigenic action of hypophysis, 155
CAMPBELL, K. R. See Bodansky, M., 684
CATCHPOLE, H. R. See Glass, S. J., 333
CAVANAUGH, L. A. See Shelton, E. K., 846
CHADWICK, C. S. See Wolfe, J. M., 503
CLARK, J. H. See Rowntree, L. G., 348
COATES, C. W. See Weisman, A. I., 561
COLLIP, J. B. See Selye, H., 667
COPPOCK, A. See Freed, S. C., 81
Corpus luteum and adrenalectomy, 550
human, progestin in, 741
Cortin, assay of extracts containing, 795
COSTELLO, J. P. Obesity and ocular symptoms in mentally alert children due to hypothyroidism, 105
Creatin and hyperthyroidism, 541
in maternal and fetal myocardium, 537
metabolism in relation to environmental temperature and thyroid function, 822

DE FREMERY, P. See Levy Simpson, S., 363
Diabetes mellitus and estrogenic hormone, 473
in pituitary infantilism, 856
treatment of, 461
DICKIE, L. F. N. See Thompson, W. O., 55
DIDDLE, A. W. See Allen, E., 546
DIDDLE, A. W. See Burford, T. H., 635
DREA, W. F. See Boissevain, C. H., 686
DUFF, V. B. See Bodansky, M., 537, 541, 822
Dwarfism, hypophyseal, 64

EINHORN, N. H., and L. G. Rowntree. The biologic effects of thymectomy, 342
ELDEN, C. A. The effects of the two ovarian hormones on castrated human females, 47
ELDEN, C. A. The pituitary-ovarian relationship in a human hypophysectomized female, 679
ELDER, J. H. See Allen, E., 546
ELLISON, E. T., and J. C. BURCH. The effect of estrogenic substances upon the pituitary, adrenals and ovaries, 746
EMERY, F. E., and E. L. SCHWABE. The rôle of the corpora lutea in prolonging the life of adrenalectomized rats, 550
dysfunction and familial hemolytic icterus, 174
glands and myopathy of nutritional origin, 393
substances, dating of, a plea for fresh products, 866
Estrin, changes in hypophysis, due to injections of, 503
effect of, 47
effect of, on pH of vaginal secretion, 210
extraction of, 224
and the menopause, 24
and menstruation, 318
and progestin therapy in prolonged anovulatory bleeding, 769
squamous metaplasia in cervical glands following administration of, 228
Estrogenic hormone, crystalline, from ovarian tissue, 563
effect, of, on blood volume, 329
effect of, on pituitary, adrenals and ovaries, 746
effect of single large dose on ovary of infantile rat, 753
evaluation of potency of, 863
in fish, 561
use of, in experimental diabetes, 473
Estrogens in urine, 546
Exophthalmic goitre, error in testing for quadriceps weakness in, 109

FALCONER, E. H. Familiar hemolytic icterus associated with endocrine dysfunction, 174
FANCHER, J. K. Hypertrophy of the testes with symptoms of hyperorchidism, 852
FENGER, F. See Andrew, R. H., 563
FERGUSON, J. Secretin XI: Its influence on the reticulocytes of the circulating blood, 683
FEVOLD, H. L. See Hisaw, F. L., 40
FIROR, W. M. See Reynolds, S. R. M., 681
FISHER, C., and W. R. INGRAM. The effect of interruption of the supraoptico-hypophyseal tracts on the antidiuretic, pressor and oxytocic activity of the posterior lobe of the hypophysis, 762
FLUHMANN, C. F. The estrin-deprivation theory of menstruation, 318
Follicular hormone and allergy, 171
FOX, C. A. See Whitehead, R. W., 93
FREED, S. C. A simple method for the extraction of both estrin and gonadotropic hormones from a single blood sample, 224
FREED, S. C., and A. COPPOCK. Fundamental similarity in the development of gonadotropic response in the immature guinea pig and rat, 81
FREED, S. C., and O. HECHTER. The extraction of both the gonadotropic and (free or total) estrogenic hormones from a single urine sample, 396
FREED, S. C., and S. SOSKIN. On the evaluation of the potency of estrogenic substances, 863
FREEMAN, H. See Hoskins, R. G., 565
FRIEDGOOD, H. B. The effect of an alkaline extract of the anterior hypophysis upon the weight of the spleen and adrenal gland and upon the blood calcium level, 159
FRIEDGOOD, H. B. Similarity of the iodin remission in experimental anterior hypophyseal hyperthyroidism, the hyperthyroidism of acromegaly and that of exophthalmic goiter, 526
FRIEDLANDER, M., N. LASKEY, and S. SILBERT. Effect of estrogenic substance on blood volume, 329

GAFFORD, J. A. See Baldwin, L. G., 373
GLASS, S. J., H. R. CATCHPOLE, and B. MCKENNON. Migraine and ovarian deficiency, 333
GOLDBERG, M. M. The treatment of pituitary infantilism with anterior pituitary extract, 854
GOLDZIEHER, M. A. Chronic hypoglycemia, 86
Gonadectomy, effect of, on hypophysis, 201
on thyroid, 201
Gonadotropic substance, effect of, on ovaries, 321
and estrin, method of extraction of from single blood sample, 224
Gonads and vitamin E, 107
GOTTLIEB, J. S. See Hoskins, R. G., 188
GRAY, P. A. The treatment of diabetes mellitus with insoluble insulin compounds, 461

HALL, B. V., and R. M. LEWIS. The induction of an acid vaginal secretion in the immature macaque by injections of oestrin, 210
HAMBLEN, E. C. The endometrium in "endometrial hyperplasia" after therapy, 769
HAMBLEN, E. C. Study of ovaries after administration of a gonadotropic principle of anterior pituitary, 321
HAMBLEN, E. C. See Pratt, J. P., 741
HAMILTON, J. B. Visceral temperatures in the

intact and unanaesthetized animal, 788
HANSON, A. M. See Rowntree, L. G., 348
HARTMAN, F. A., and W. D. POHLE. Extracts containing cortin, 795
HAYWARD, S. J. See Loeb, L., 511
Heat production, effect of endocrine extracts on, 1
HECHTER, O. See Freed, S. C., 396
HERRMANN, C. L. See Bodansky, M., 684
HERTZ, S., and E. G. OASTLER. Assay of blood and urine for thyreotropic hormone in thyrotoxicosis and myxedema, 520
HERTZ, R. See Hisaw, F. L., 40
HERTZ, S. See Horton, J. W. 831
HISAW, F. L., R. HERTZ and H. L. FEVOLD. Experimental production of ovarian refractoriness to anterior hypophyseal stimulation in the monkey, 40
HISAW, F. L., and F. C. LENDRUM. Squamous metaplasia in the cervical glands of the monkey following oestrin administration, 228
Hormone in saliva, 103, 864
HORTON, J. W., and SAUL HERTZ. The significance of electrical impedance measurements on the human body, 831
HORTON, J. W., A. C. VANRAVENSWAAY, S. HERTZ and G. W. THORN. The clinical significance of electrical impedance determination in thyroid disorders, 72
HOSKINS, R. G., and H. FREEMAN. Weight changes following the use of glycerin extract of adrenal cortex, 565
HOSKINS, R. G., and J. S. GOTTLIEB. Is the pressor effect of glycerin extract of adrenal glands due to epinephrine? 188
HUNTER, W. C. See Myers, H. B., 389
Hyperorchidism and testicular hypertrophy, 852
Hypertension and prolan excretion, 180
Hypoglycemia and hypophysis, 86
and thyroid insufficiency, 86
Hypophyseal cachexia, 155
following acromegaly, 846
metabolic study of case of, 137
dwarfism, metabolic study of case of, 137
infantilism, treated with anterior pituitary extract, 854
with diabetes mellitus, 856
Hypophysectomy, changes in muscle chemistry after, 184
changes in pancreas and liver after, 496
composition of weight lost, after, 489
effect of, on nitrogen, calcium and phosphorus metabolism, 481
nitrogen partition of tissue after, 489
simple method, of, in dog, 860
Hypophysis and allergy, 171
calorigenic action of, 1
calorigenic action of, 55
effect of estrin injections on, 503
effect of estrogenic substances on, 746
effect of estrogenic substance on, in large doses over varying periods, 753
effect of interruption of supraoptico-hypophyseal tracts on posterior lobe of, 762
extract in endocrine dwarfism, 64
gonadotropic principle of, 321
and hypoglycemia, 86
ovarian refractoriness to anterior extract of, 40
and ovary, 511
relation of, to thyroid and ovary, 511
Hypothyroidism in children, 105, 816

Icterus, hemolytic and endocrine dysfunction, 174
Impedance, electrical, and thyroid disease, 831
INGRAM, W. R. See Fisher, C., 762
Insulin, insoluble compounds of, 461
Internal impedance and thyroid disorders, 72
Iodin remission in thyroid disease, 526
ISREAL, S. L. See Mazer, C., 753
ISRAEL, S. L. See Scarf, M., 180

JOHNSON, G. E. See Baker, B. L., 219

KAMM, O. See Pratt, J. P., 741
KERLEY, C. G. Childhood myxedema. Observations through infancy, childhood and early adult life, 611
KIPPEN, A. A., and L. LOEB. The effect of gonadectomy on the thyroid gland in the guinea pig, 201
KURZROK, R. See Solomonica, B., 171

LAHR, E. L. See Riddle, O., 1
LASKEY, N. See Friedlander, M., 329
LEE, M., and G. B. AYRES. The composition of weight lost and the nitrogen partition of tissues in rates after hypophysectomy, 489
LENDRUM, F. C. See Hisaw, F. L., 228
LERMAN, J. See Salter, W. T., 801
LEVY SIMPSON, S., P. DE FREMERY and A. MACBETH. The presence of an excess of male (comb-growth and prostate-stimulating) hormone in virilism and pseudohermaphroditism, 363
LEWIS, R. M. See Hall, B. V., 210
LISSER, H. A case of adrenal cortical tumor in an adult male causing gynecomastia and lactation, 567
Liver, effect of hypophysectomy and phyone on, 496
LOEB, L. See Kippen, A. A., 201
LOEB, L., J. SAXTON and S. J. HAYWARD. The relationship of the anterior pituitary gland to thyroid and ovary, 511

MACBETH, A. See Levy Simpson, S., 363
Male hormone, in virilism and pseudohermaphroditism, 363
MARCUS, I. H. Short stature of patient—A cause of error in performing Plummer's test for quadriceps weakness in exophthalmic goitre, 109
MARENZI, A. D. Chemical changes in the muscle of the hypophysectomized toad, 184
MARLOW, H. W. The effect of injection of residual ovarian extracts, 339
MAZER, C., S. L. ISRAEL and B. J. ALPERS. The time element in the pituitary-ovarian response to large doses of the estrogenic hormone, 753
MCGINTY, D. A. See Pratt, J. P., 741
MCKENNON, B. See Glass, S. J., 333

McMANUS, M. A. See Rowe, A. W., 648
Menopause and ovarian dysfunction, 24
Menstruation, estrin deprivation theory of, 318
Metabolism, changes in, following hypophysectomy, 481
Migraine and ovarian deficiency, 333
MOEHLIG, R. C. Pituitary cachexia (Simmonds' disease). Report of a case in which the patient failed to respond to various forms of endocrine therapy, 155
MOLITCH, M., and S. POLIAKOFF. Subclinical hypothyroidism in children, 816
MORAN, C. S. See Riddle, O., 1
MORGULIS, S., and H. C. SPENCER. A note on the condition of the endocrine glands in myopathy of nutritional origin, 393
MOSES, R. L. See Weisman, A. I., 561
MYERS, H. B., B. VIDGOFF, G. H. SCHADE and W. C. HUNTER. Prostatic atrophy following testicular feeding, 389
Myopathy of nutritional origin, 393
Myxedema, human, assay of artificial thyroid protein in, 801

NADLER, S. B. See Thompson, W. O., 55
NELSON, W. O., and M. D. OVERHOLSER. The effect of oestrogenic hormone on experimental pancreatic diabetes in the monkey, 473
NEUHOFF, F. See Sexton, D. L., 856
NEUSTAEDTER, T. A modification of the Frank-Goldberger blood estrin test, 639
Nitrogen metabolism in relation to environmental temperature and thyroid function, 822
NORRIS, E. R. See Weiser, R. S., 556

OASTLER, E. G. See Hertz, S., 520
Obesity and hypothyroidism in children, 105
Ocular symptoms and hypothyroidism in children, 105
ORGEL, M. N., and D. BARR. Thyroid dysfunction in hemochromatosis, 839
Osseous retardation in diagnosis of hypothyroidism in children, 816
Ovarian deficiency and migraine, 333
Ovarian extracts, residual, effect of, 339
Ovariectomy and uniformity of uterine and body temperatures, 788
Ovary, dysfunction of, 24
effect of dinitrophenol and thyroid on, 456
effect of estrogenic substances on, 746
effect of estrogenic substance on, in large doses over varying periods, 753
refractoriness to anterior hypophysis extract, 40
stimulation of, by anterior pituitary extract, 321
OVERHOLSER, M. D. See Nelson, W. O., 473
OWEN, S. E. The reaction of fish to sex hormones, 214
Oxytocic activity of posterior lobe, effect of interruption of supraoptico-hypophyseal tracts on, 762

Paget's disease, 226
Pancreas, effect of hypophysectomy and phyone on, 496
PATEK, P. R. See Shelton, E. K., 847
PERLA, D., and M. SANDBERG. The effect of complete and partial hypophysectomy in adult albino rats on nitrogen, calcium and phosphorus metabolism, 481
Pineal extract, effect of, 348
Pitocin, effect of, on uterus, 17
use of, in diagnosing pelvic conditions, 17
PLUMMER, A. J. See Rowe, A. W., 648
POHLE, W. D. See Hartman, F. A., 795
POLIAKOFF, S. See Molitch, M., 816
PRATT, J. P., E. C. HAMBLEN, O. KAMM and D. A. McGINTY. The human corpus luteum and progestin, 741
PRATT, J. P. See White, M. R., 17
Pregnancy, effect of pitocin on uterus in, 17
and thyroxin resistance, 537
urine extract and allergy, 171
urine extract in treatment of undescended testes, 192
urine, response of immature guinea pigs and rats to, 81
urine, treatment of sexual underdevelopment with A.P.L. hormone of, 781
Pressor activity of posterior lobe, effect of interruption of supraoptico-hypophyseal tracts on, 762
Progestin in blood, 307
effect of, 47
and estrin therapy in prolonged anovulatory bleeding, 769
from human corpus luteum, 741
Prolan A and the menopause, 24
Prostate, effect of testicular feeding on, 389
Pseudo-hermaphroditism, male hormone in, 363

RASMUSSEN, A. T. The relation of the basophilic cells of the human hypophysis to blood pressure, 673
Reid Hunt reaction and follutein, 100
REYNOLDS, S. R. M., W. M. FIROR and W. M. ALLEN. Relative effectiveness of progestin in hypophysectomized and normal rabbits, 681
RICHTER, C. P. The spontaneous activity of adrenalectomized rats treated with replacement and other therapy, 657
RIDDLE, O., G. C. SMITH, P. W. BATES, C. S. MORAN and E. L. LAHR. Action of anterior pituitary hormones on basal metabolism of normal and hypophysectomized pigeons and on a paradoxical influence of temperature, 1
RILEY, G. A. See Rowe, A. W., 648
ROSE, E., and G. WEINSTEIN. Cachexia hypophyseopriva (Simmonds' disease) with thyroid and suprarenal insufficiency, 149
ROWE, A. W., M. A. McMANUS, A. J. PLUMMER and G. A. RILEY. The metabolism of levulose: The influence of endocrine dysfunction on tolerance, 648
ROWNTREE, L. G., J. H. CLARK, A. STEINBERG and A. M. HANSON. The biological effects of pineal extract (Hanson), 348
ROWNTREE, L. G. See Einhorn, N. H., 342
RUBINSTEIN, H. S. The difference of response of males with undescended testes to the water soluble (anterior pituitary-like) fraction of pregnancy urine, 192

Saliva, hormone content of, 103
SALTER, W. T., and J. LERMAN. The genesis of thyroid protein: clinical assays of artificial thyroid protein in human myxedema, 801
Salts, effect of, on survival after adrenalectomy, 556
SANDBERG, M. See Perla, D., 481
SAPHIR, W. Vitamin E and the gonads, 107
SAXTON, J. See Loeb, L., 511
SCARF, M., and S. L. ISRAEL. Excretion of prolan in essential hypertension, 180
SCHADE, G. H. See Myers, H. B., 389
SCHAEFER, R. L. Endocrine dwarfism, 64
Schizophrenia, treatment in, with glycerin extract of adrenals, 188
SCHWABE, E. L. See Emery, F. E., 550
SELYE, H., and J. B. COLLIP. Fundamental factors in the interpretation of stimuli influencing endocrine glands, 667
SEVRINGHAUS, E. L. Practical sex hormone therapy, 230
Sex hormone, assay of, 214
therapy, 230
SEXTON, D. L. Treatment of sexual underdevelopment in the human male with the anterior-pituitary-like hormone (A.P.L.) of pregnancy urine, 781
SEXTON, D. L., and F. NEUHOFF. Pituitary infantilism with diabetes mellitus, 856
Sexual underdevelopment treated with A.P.L. hormone of pregnancy urine, 781
SHELTON, E. K., L. A. CAVANAUGH and P. R. PATEK. Fugitive acromegaly. Acromegaly followed by pituitary cachexia, 846
SILBERT, S. See Friedlander, M., 329
Simmonds' disease, report of a case of, 149, 155
Skeletal muscle, changes in chemistry of, after hypophysectomy, 184
SMITH, G. C. See Riddle, O., 1
SOLOMONICA, B., and R. KURZROK. The influence of endocrine gland preparations on allergic reactions (anterior pituitary extract, pregnancy urine extract, follicular hormone), 171
SOSKIN, S. See Freed, S. C., 863
Spleen, effect of alkaline extract of anterior hypophysis upon, 159
SPENCER, H. C. See Morgulis, S., 393
STEINBERG, A. See Rowntree, L. G., 348
SUSMAN, W. Atrophy of the adrenals and Addison's disease, 383

TAYLOR, S. G., III. See Thompson, W. O., 55
Temperature, environmental, and survival after adrenalectomy, 556
Testes, hypertrophy of, and hyperorchidism, 852
Testicular feeding, effect on prostate, 389
Theelin and uniformity of uterine and body temperatures, 788
THOMPSON, J. The influence of the intake of calcium on the blood iodine level, 809
THOMPSON, P. K. See Thompson, W. O., 55
THOMPSON, W. O., S. G. TAYLOR, P. K. THOMPSON, S. B. NADLER and L. F. N. DICKIE. The calorigenic action of extracts of the anterior lobe of the pituitary in man, 55
THORN, G. W. Creatine studies in thyroid disorders, 628
THORN, G. W. See Horton, J. W., 72
Thymectomy, effects of, 342
Thyrotropic hormone, assay of, in myxedema and thyrotoxicosis, 520
and Reid Hunt reaction, 100
Thyroid disease, assay of thyrotropic hormone in, 520
disease and iodin remission, 526
disease, iodin tolerance test in, 358
disorder and electrical impedance, 72, 831
dysfunction in hemochromatosis, 839
function, nitrogen and creatine metabolism in relation to, 822
gland, effect of estrogenic substances on, 746
gland, effect of estrogenic substance on, in large doses over varying periods, 753
gland, effect of gonadectomy on, 201
protein, assay of artificial, in human myxedema, 801
Thyroxin resistance and age, 541
and pregnancy, 537
TWOMBLY, G. H. Studies of the nature of antigonadotropic substances, 311

Urine, estrogens in, 546
extraction of gonadotropic and estrogenic hormones from, 396
Uterine and body temperatures, uniformity in, 788

Vaginal secretion, changes in, after estrin, 210
VANRAVENSWAAY, A. C. See Horton, J. W., 72
VIDGOFF, B. See Myers, H. B., 389
Virilism, male hormone in, 363
Vitamin E, assay of, 107

WARD, E. N. See Adams, A. E., 496
WATSON, E. M., and A. S. BARBER. An iodine tolerance test for the investigation of thyroid function, 358
WEINSTEIN, G. See Rose, E., 149
WEISER, R. S., and E. R. NORRIS. The influence of environmental temperature and salts upon the survival period of adrenalectomized rats, 556
WEISMAN, A. I. Further investigation of the hormone content of saliva using the female bitterling test, 864
WEISMAN, A. I., C. W. COATES and R. L. MOSES. An investigation of the presence of estrogenic hormones in the ova and ovaries of fish, 561
WEISMAN, A. I., and C. C. YERBURY. An investigation of the hormone content of saliva, 103
WHITE, M. R., and J. P. PRATT. Uterine response to pitocin, 17
WHITEHEAD, R. W., and C. A. FOX. The influence of cortico-adrenal extract on the course of bacterial intoxications in guinea pigs, 93
WHITNEY, R., and H. O. BURDICK. Tube-

locking of ova by oestrogenic substances, 643
WIESBADER, H. Reid Hunt reaction and the thyrotropic hormone, 100
WOLFE, J. M., and C. S. CHADWICK. Quantitative studies on the structural changes induced in the anterior hypophysis by injections of oestrin, 503
YERBURY, C. C. See Weisman, A. I., 103

ABSTRACTS

ABELIN, I. Tyrosine and thyroxin, 453
ABERCROMBIE, W. F., W. H. CRANE and J. C. BRAKEFIELD. The morphological effects of excess amounts of iodine on the thyroid gland of the cat, 290
Abortion and diabetes, 730
  folliculin and corpus luteum in, 424
  habitual, and hypophyseal insufficiency, 435
ABERLE, S. B. D. See Landauer, W., 576
Acetylcholine, effect of, on pulmonary blood vessels, 403
  effect of, on epinephrine output, 405
  effect of, on isolated fallopian tube, 419
  effect of, on submaxillary gland, 404
  and insulin, 729
Acid, effect of, on gonadotropic hormone, 437
Acne vulgaris, effect of anterior pituitary-like hormone, on, 593
Acromegaly, effect of urine from, on growth, 127
  and osteoporosis, 700
  Acroparesthesia, treatment of, 417
Addison's disease and adrenal atrophy, 697
  and adrenal denervation in diabetes mellitus, 694
  blood sodium in, 115, 874
  cholesterinemia in, 245
  effect of adrenalin in, 402
  hypophysis in, 691
  incidence, diagnosis and treatment, 116
  possible causes of, 116
  retention of Vitamin C in, 115
  salt treatment in, 246
  and sulphur metabolism, 701
  symptoms of, 697
  treatment of, 696
  tuberculosis in, 246
Adenoma of parathyroid, 451
Adrenal atrophy and Addison's disease, 697
  cause of, 696
Adrenal cortex, accessory bodies of, 693
  action of urine principle of cancer patient on, 239
  and anterior hypophysis, 271
  atrophy of, 876
  and carbohydrate formation, 403
  carcinoma of and hirsutism and hypertension, 875
  crystalline substances from, 875
  and body temperature, 697
  effect of vitamins A and C on, 574
  extract, antagonist to iodacetic acid poisoning, 693
  extract and ascorbic acid, effect of, on muscle activity, 239
  extract, assay of, 116, 245
  extract, chemical nature of, 694
  extracts, crystalline compounds in, 248
  extracts, distribution in solvents, 245
  extract, effect of, on adrenalin secretion, 697
  extract, effect of, on thyroid hyperactivity, 240
  extract and experimental neurosis, 693
  extract, influence of, on resistance to toxins, 570
  extract, influence of, on thyroid-stimulating principle of hypophysis, 240
  extract, methods of preparation, 116
  extract, new test for, 405
  extract, oral administration of, 114
  extract, relation of, to nitrogen metabolism, 115
  extract, titration of, by resistance to morphine, 243
  extract in vomiting of pregnancy, 247
  and glutathione, 240
  influence of sex hormone on, 252
  and insulin, 695
  morphology, study of, 697
  relation to reproduction and lactation, 874
  and vitamin C, 876
  cortical carcinoma with Cushing's syndrome, 692
  cortical cells in epididymis, 243
  cortical hyperfunction, 404
  cortical insufficiency, mechanism of, 114
  cortical neoplasms and hypophysis, 404
  cortical syndrome, 696
  cortical tumor, in boy of five years, 244
  cortical tumor, test for, 571
  cortico-genital syndrome and pituitary basophilic syndrome, 243
  deficiency and galactose metabolism, 408
  deficiency, sodium chloride therapy in, 115
  denervation and diabetes mellitus, 694
  extract and diuresis, 407
  extracts, inactive crystalline compounds from, 245
  extracts, methods of fractionation of active principle, 245
Adrenal glands, accessory, 243
  adrenin content of, after lower spinal cord destruction, 571
  adrenin content of, after parathyroid ablation, 239
  and alarm reaction, 876
  and diabetogenic action of anterior hypophysis, 589
  and diabetes mellitus, 698
  diseases of, 242
  effect of gonadectomy on, 877
  effect of large doses of vitamin A on weight of, 451
  effect of stimulation on content of, 692
  effect of thyroid on ascorbic acid content of, 459
  enlargement of, after injection of thyrotropic hormone, 605
  and female reproductive system, 691
  and glutathione, 693
  and hypertension, 406, 693, 874
  in hypoglycemia, 731
  innervation of, 877
  iodine in, 240
  and lactation, 874, 875
  medullary tumor of, 692
  neuroblastoma of, in children, 570
  and pigmentation, 405
  and prolonged administration of estrin, 711
  retention of Vitamin C and, 115
  and salt metabolism, 115
  survival and increase of epinephrine in tissue cultures of, 244
  tuberculosis of, 246
  vitamin C content of, after thyroid feeding, 302
  x-ray demonstration of, 403
  grafts, effect of, on work capacity in adrenalectomized rats, 242
  grafts from newborn into adults, 695
  innervation and adrenalin secretion, 694
  insufficiency, 405, 694
  insufficiency, role of hypophysis in, 571
  insufficiency, sodium in, 244
  insufficiency, water loss in, 241
  medulla, stimulation of, by irradiated insulin, 244
  medulla, work capacity after destruction of, 242, 692
  medulla, vitamin C in, 241
  medulla, voluntary activity after destruction of, 692
  and ovary ablation, effect of, on estrus, 119
  pathology in Addison's disease, 116
  secretion, action of atropin on, 572
  tumor and cerebral hemorrhage, 572
  tumor and increased blood pressure, 572
  tumor and pubertas praecox, 572
  virilism, Cushing's disease and constitutional obesity, 272
  weight, effect of exhaustion on, 573
Adrenalectomy, action of adrenin after, 242
  and adrenal cortical hyperfunction, 404
  and asthenia, 691
  cortical hormone requirement after, 245
  deciduoma reaction after, 423
  effect of, on absorption, 696
  effect of adrenalin on blood sugar after, 402
  effect of, on gonads and accessory organs, 246
  effects of, in male rats, 246
  effect of, on rat incisors, 695
  fetal carbohydrate metabolism following, 113
  in frogs, general character of syndrome, 693
  glucose metabolism after, 572, 876
  and hypertension, 113
  incapacity to work, after, 241
  and metabolism of excised tissues, 571
  and nitrogen metabolism, 695
  and pancreatectomy in the dog, 132
  and parathyroid glands, 695
  pathological changes after, 875
  salt-treatment after, 404

and sulfur metabolism, 695
use of adrenal cortex extracts after, 246
in young rats, 246
Adrenalin, action of, on melanophore system, 573
action of, on respiratory quotient, 403
and bile composition, 699
and blood sugar, 575, 875
effect of, on blood sugar and lactic acid in Addison's disease, 402
effect of, on paralytic submaxillary gland, 404
effect of, on peripheral sugar, 130
effect of, on pulmonary blood vessels, 403
effect of, on sex function after adrenolectomy, 246
effect of, on sulfur metabolism, 407
effect of thyroid on calorigenic action of, 698
and blood vessels, 703
and carbohydrate metabolism, 403
and cholin, chemical relationship of, 696
effect of, on blood lipoids, 691
effect of cortain on secretion of, 697
effects of, in moderate work, 114
and follicle solution, 372
and insulin in treatment of diabetes, 596
intravenous and intra-arterial injection of, 239
and recovery from ventricular fibrillation, 876
secretion and denervation of adrenals, 246
and vascular response to sympathetic stimulation, 113
-like substance in autolyzing adrenal glands, 875
-like substance in liver extract, 575
Adrenalinogenous cells, incretory vacuoles in, 573
Adrenergic dilator mechanism, depression of, 116
Adrenin, action of, after adrenalectomy, 242
and blood sugar, 402
differential depression of vasomotor mechanisms by, 116
effects of, on iris and nictitating membrane, 113
and shock, 239
Adrenotropic hormone of hypophysis, 124
in Cushing's Disease, 126
Age relation of, to sex inversion, 705
AITKEN, R. S., and D. S. RUSSELL. A case of Simmonds' syndrome, 262
AKEL, J. See Lipschütz, A., 593
ALBRIGHT, F., and E. BLOOMBERG. Hyperparathyroidism and renal disease, 447
ALBRIGHT, F., E. BLOOMBERG, B. CASTLEMAN and E. D. CHURCHILL. Hyperparathyroidism due to diffuse hyperplasia of all parathyroid glands rather than adenoma of one; clinical studies on three such cases, 133
ALBRIGHT, F., J. A. HALSTEAD and E. CLONEY. Studies on ovarian dysfunction, 248
ALDRICH, C. A., and J. A. WALSH. Cachexia hypophyseopriva (Simmonds' disease). Report of a case in an adolescent girl, 602
ALEXANDER, B. See Ernestene, A. C., 597
Alfalfa, gonad-stimulating extract from, 254
Alkali, effect of, on gonadotropic hormone, 437
Allen-Doisy test, biology and technic of, 582
ALLEN, E., and A. W. DIDDLE. Ovarian follicular hormone effects on the ovaries, 576
ALLEN, E. Menstruation, 248
ALLEN, E. See Gardner, W. U., 705
ALLEN, E. See Hill, R. T., 707
ALLEN, R., and G. BOURNE. An extract from the adrenal gland causing luteinisation of the ovaries and endometrial hyperplasia, 691
ALLEN, W. M., A. BUTENANDT, G. W. CORNER and K. H. SLOTTA. Nomenclature of corpus luteum hormone, 576
ALLEN, W. M., and R. K. MEYER. Physiology of the corpus luteum; the inhibition of oestrin by progestin-containing extracts of corpus luteum, 409
ALLEN, W. M. The isolation of crystalline progestin, 248
ALLIEZ, J. See Rover, H., 701
ALLOT, E. N. Chemical changes in the blood in Addison's disease, 874
ALPERS, B. J. See Mazer, C., 690
ALTSCHUL, A. Treatment of dysmenorrhea with insulin, 698
ALSINA, F. D. The production of adrenin in shock and its part in vasconstriction to protect against low blood pressure, 239
Aluminum hydroxide, adsorbtion of gonadotropic hormone by, 705
Amenorrhea and adrenal cortical hyperfunction, 404
treatment of, 120, 418
Amino nitrogen in blood after glucose, 244
Amniotin, its use in specific and nonspecific vaginitis, 119
ANDERSEN, D. H. See Victor, J., 726
ANDERSEN, T. T. Observations on insulin-adrenalin treatment by the Clausen method, 596
ANDERSON, D. H. The effect of food and of exhaustion on the pituitary, thyroid, adrenal and thymus glands of the rat, 573
ANDERSON, E. M. See Collip, J. B., 124
ANDERSON, E., and W. HAYMAKER. Elaboration of hormones by pituitary cells growing in vitro, 262
ANDERSON, E. See Pugsley, L. I., 302, 736
ANDERSON, I. Effect of adrenalin on blood sugar and lactic acid in Addison's disease and in adrenalectomized dogs, 402
ANDERSON, J. A. See McQuarrie, I., 731
ANDERSON, O. D. See Liddell, H. S., 693
Androstane-diol, assay in rats, 710, 711
physiological action of, on capons, 412
Androsterone, effects on comb growth, 417
action of, 434
effect of, on chick embryos, 716
isolation of, 578
group, comparative activities of, 414
group, new synthetic members of, 411
in normal male urine, 412
synthetic, 709
ANDRUS, E. C., and D. MCEACHERN. Studies on the increased metabolism in hyperthyroidism, 453
ANDRUS, W. D. See Heuer, G. J., 241
Angina pectoris, reduction of blood supply of thyroid in, 608
thyroidectomy in, 736
total thyroidectomy in, 604
ANKER, H., and P. LALAND. Hormone investigations in pernicious vomiting of pregnancy, 427
ANSCHEL, E. See Sainton, P., 303
ANSELMINO, K. J., L. HEROLD, F. HOFFMAN and R. I. PENCHARZ. Studies on the physiology of lactation. III. The inhibitor for lactation, 409
ANSELMINO, K. J., and F. HOFFMAN. Concerning the effects of anterior lobe substances on blood sugar, 262
ANSELMINO, K., and F. HOFFMAN. Preparation of the fat metabolism hormone of the anterior hypophysis, 716
ANSELMINO, K. J., and F. HOFFMAN. Studies on the physiology of lactation. IV. Inhibition of lactation by follicular hormone, 577
Anterior hypophysis-like hormone, in menorrhagia and metrorrhagia, 255
principle of pregnancy urine, use of, in Simmonds' disease, 270
principle, physiologic properties of, 265
hormone, relation of potency of, to pH, 267
Anterior-posterior lobe antagonism, 128
Antianemic principle of liver, effect of, 702
Antidiuretic action of hypophysis extract, 127
factor in cerebrospinal fluid, 586
Anti-gonadotropic sera, immunologic studies of, 263
substances and 'constant' estrus, 432
Anti-substances and ovary-stimulating factors, 268
Anti-thyroid substance and lactation, 702
Anti-thyrotropic activity of normal blood, 293
factor, formation of, 594
Anti-thyroid substances, effect of, on serum lipase, 296
Antuitrin S, effect of, on male lizard, 432
effect of, on ovary, 719, 721
treatment of undescended testes, 714
ARON, M. Injections of extract of the anterior hypophysis into foetal guinea pigs in utero. Action on the gonads, 262
ARON, M. Injections of extract of the anterior hypophysis into guinea pigs in utero. Action on the islet tissue of the pancreas, 284
ARON, M. New technical methods for demonstrating a principle in the urine of cancer patients which reacts on the adrenal cortex, 239
ARON, M. The presence in the urine of cancerous patients of an increased amount of 'gondo-stimulin,' 263
Arrhenoblastoma; a special type of teratoma, 712
ARSAMASZEVA, N. See Raspopova, N. A., 737
Arterial hypertension and the menopause, 414
Arteriosclerosis in diabetes mellitus, 598
Arthritis, and thyroid disease, 459
Artificial light, action of, on hypophysis and testis, 429
ARTUNDO, A. See Houssay, B. A., 271
ASCHHEIM, S., and H. GESENIUS. Effect of sex hormone on the metabolism of the sex organs, 577
Aschheim-Zondek test, Friedman's modification of, 268
Aschheim-Zondek test, value of, 419
Ascorbic acid and adrenals, 692

and cortical hormone, 239
metabolism and thyroid hormone, 459
new test for, 405
ASIMOFF, G., V. PTCHELINA and N. PARIJSSKAYA. Effect of extracts of anterior pituitary and of prolan on lactation, 585
ASIMOFF, G. S. See Zavadovsky, B. M., 426, 728
ASKIN, J. A., and J. GESCHICKTER. Neuroblastoma of the adrenal in children, 570
Assay of thyrotropic hormone, 725
Assays of adrenal cortex hormone, 697
Asthenia and hypophysis, 266, 283
ATCHELY, D. W. See Loeb, R. F., 244
ATCHLEY, D. W. See Stahl, J., 405
ATKINSON, A. J., and A. C. IVY. Menstrual edema: Report of case controlled by emmenin but not by theelol or theelin, 577
Atropin, action of, on adrenal secretion, 572
ATWELL, J. Differentiation and function of heterotoptic autoplastic transplants of the amphibian hypophysis, 427
ATWELL, W. J. Effects of thyreotropic and adrenotropic hormones on hypophysectomized frog tadpoles, 122
ATWELL, W. J. Effects of thyreotropic and adrenotropic principles on hypophysectomized amphibia, 428
AUB, J. C. Parathyroid hormone therapy, 447
AUBERTIN, E., and E. CASTAGNOU. Hypoglucemic action of insulin in dogs with ligated pancreatic ducts and with or without secondary fatty degeneration of the liver, 729
AUBERTIN, E., A. LACOSTE, R. SARIC and E. CASTAGNOU. Functional and anatomical state of the islets of the pancreas and their insulin content in fasting dogs, 729
AUBRUN, E. A. Cutaneous symptoms in hypophysectomized toads, 263
Auricular fibrillation, influence of age on, in hyperthyroidism, 457
Antidiuretic substance and hypertension, 436
Autonomic nervous system and pigmentation, 405
stimulation and carbohydrate metabolism, 125

BACHMAN, C. Immunologic studies of antigonadotropic sera, 263
BACHMAN, C., J. B. COLLIP and H. SELYE. Antigonadotropic substances, 263
BAENA, V. Effect of the cortical hormone and of ascorbic acid on the biochemical conditions of muscle activity, 239
BANCROFT, I. Pigmentation of metabolic origin: Its relation to the autonomic nervous system, 405
BANNET, I. See Glaser, E., 130
BARKER, S. B., J. F. FAZIKAS and H. E. HIMWICH. Metabolic aspects of thyroid-adrenal interrelationship, 698
BARKER, S. B. See Himwich, H. E., 571
BARNES, B. O. See Mathieu, F., 421
BARNES, B. O. See McLean, F. C., 133
BARRON, L. E. See Curtis, G. M., 734
Basal metabolism and blood cholesterol in hyperthyroidism and hypothyroidism, 458
and hypophysis, 271
and menstrual disturbances, 295
new standards for girls, 703
and thyroid, 135, 271, 457
effect of thyrotropic hormone on, 128
effect of thyroxin on, 298
Basedow's disease, animal blood in, 604
non-operative therapy of, 456
Basophil adenoma of hypophysis and adrenal cortical carcinoma, 692
Basophilism, hypophyseal, 123, 130, 593
BASTAI, P., and G. C. DOGLIOTTI. Hyperparathyroidism and angiospastic syndromes, 133
BASTENIE, P., and G. ROOST. Functional significance of the interstitial islets in the thyroid of the guinea pig, 602
BATES, R. W. See Riddle, O., 280, 596
BATES, R. W., T. LAANES and O. RIDDLE. Evidence from dwarf mice against the individuality of growth hormone, 428
BATES, R. W., E. L. LAHR, and O. RIDDLE. The gross action of prolactin and follicle-stimulating hormone on the mature ovary and sex accessories of fowl, 428
BATES, R. W., and O. RIDDLE. The preparation of prolactin, 263
BATES, R. W., O. RIDDLE and E. L. LAHR. An assay of three hormones present in anterior pituitaries of seven types of cattle classified for age, sex and stage of reproduction, 122
BAUCH, M. Diabetes mellitus as influenced by psychophysical practice, 442
BAUDOUIN, A., H. BÉNARD, J. LEWIN and J. SALLET. Intravenous and intra-arterial injections of adrenalin. Effect on arterial pressure, 239
BAUDOUIN, A., H. BÉNARD, J. LEWIN and J. SALLET. Slow and continuous injections of adrenin. Relation between dosage and degree of glycemia, 402
BAUER, C. P. See Kanter, A. E., 709
BAUM-MENENDEZ, E. Reaction of hypophysectomized dogs to the hypotension following bleeding, 264
BAYER, L. M., and H. GRAY. Obesity treatment by diet, thyroid and dinitrophenol; result on 106 outpatients, 134
BEALL, D., and M. EDSON. Some notes on the isolation of oestrone and equilin from the urine of pregnant mares, 878
BEAUNE, A. See Broun, D., 729
BEAUX, A. R. Glutathione of red blood cells in hyper and hypothyroidism, 602
BECK, E. C., J. G. FOWLER, E. KOENIG and B. D. BOWEN. Vascular disease in the obese diabetic and in non-diabetics; A discussion of arteriosclerosis as a cause of diabetes, 442
BEEKHUIS, W. H. Dangers in the treatment of exophthalmic goiter by di-iodotyrosine, 602
BEETHAM, W. P. See Waite, J. H., 598
BEILESS, I. See Landau, A., 131
BELKIN, R. Influence of hypophyseal extract on regeneration in axolotls, 264
BELL, M. A. See Dannenberg, A. M., 729
BELTRAMETTI, L. Sexual functions in relation to water economy, especially to diabetes insipidus, 428
BÉNARD, H. See Baudouin, A., 239, 402
pressure and hypophysis, 436, 595, 721
BENAZZI, M. The follicular hormone inhibits the function of the thyroid, 602
BENETATO, G., I. GAINA and C. OPRISIU. Influence of induced adrenal cortical hypertrophy and of cortical extract on resistance to certain toxins, 570
BENITEZ, J. See Marañon, G., 245
BENOIT, J. Effect of natural light on testicular growth in ducks, 577
BENOIT, J. Hypophysectomy and artificial illumination in the male duck, 717
BENOIT, J. Induction of sexual maturity and ovulation in domestic ducks by exposure to light, 578
BENOIT, J. Part played by the hypophysis in the stimulation of the testis by artificial light, 429
BENOIT, J. The rôle of the eyes in the stimulating action of artificial light on the testis, 410
BENOIT, J. Stimulation by artificial light of testicular development in ducks with sectioned optic nerves, 577
BENOIT, J. Stimulation by artificial light of testicular development in ducks with enucleated eyes, 578
BENOIT, J. Stimulation of testicular development by artificial illumination, 409
BENOIT, J. Testicular growth in the immature duck stimulated by artificial light. Histological study, 703
BENOIT, W. Hyperinsulinism accompanying congenital atresia of the pancreatic ducts, 443
BENNETT, R. J., Jr. A simple method of hypophysectomy in the dog, 688
BEHRLINGER, W. Basophile cells of the adenohypophysis and the neurohypophysis in essential hypertension and eclampsia, 439
BERGAUER, V., J. BOUCEK and V. PODROUZEK. Changes in the chloride ion concentration in blood serum under the influence of the thyroid and the hypophysis, 291
BERGAUER, V., V. STICH and Z. ZLABEK. Sodium chloride crystallization in pregnant women, 573
BERGMANN, F. Effect of pregnyl on pregnant rats, 585
BERLIN, D. D. Total thyroidectomy for intractable heart disease: Summary of two and one-half years' surgical experience, 603
BEST, B. D. A case of granulosa-cell carcinoma of the left ovary in a child of six years, 410
BIALET-LAPRIDA, Z. The desensitization of the ovary to the action of folliculin, 248
BIALET-LAPRIDA, Z. Habituation of the ovaries to folliculin injections, 249
BIASOTTI, A. Glucose consumption by hypophysectomized pancreatectomized dogs, 585
BIASOTTI, A. Glucose tolerance and hypophyseal deficiency, 123
BIASOTTI, A. Glucose tolerance of hypophysectomized dogs, 585
BIASOTTI, A. See Houssay, B. A., 125, 242, 589, 721

BIGGART, J. H. Some observations on the basophil cells of the human hypophysis, 429
BISGARD, J. D. See Sharpe, J. C., 739
BISHOP, P. M. F., F. COOK and A. C. HAMPSON. Indications for the clinical use of progestin, 703
BINET, L., and G. WELLER. The adrenin content of the adrenals in parathyroidectomized animals, 239
BINNING, G. The incidence of goiter amongst Saskatoon school children, 603
BISCHOFF, F. The influence of divided dosage of gonadotropic extracts in the male rat, 429
BISCHOFF, F. See Maxwell, L. C., 289, 437
BISKIND, G. R., and D. GLICK. Studies in histochemistry. V. The vitamin C concentration of the corpus luteum with reference to the stage of the estrous cycle and pregnancy, 410
BISSONNETTE, T. H. Modification of mammalian sexual cycles; reversal of the cycle in male ferrets (Putorius vulgaris) by increasing periods of exposure to light between October 2nd and March 30th, 410
BISSONNETTE, T. H. Relations of hair cycles in ferrets to changes in the anterior hypophysis and to light cycles, 429
BISWANGER, F. Studies on the physiology of the thyroid. Sensitivity of thyroxin, 733
BISWANGER, F. Studies on the physiology of the thyroid, 733
BLOCK, R. J. See Brand, E., 430
BLOOD, amino nitrogen content of, after glucose, 244
calcium in pancreatectomized and hypophysopancreatectomized dogs, 286
cholesterol and basal metabolism in hyperthyroidism and hypothyroidism, 458
effect of hypophysectomy on, 441
fat tolerance tests in malnutrition and obesity, 123
fluorine in, 455
gonadotropic content of, in normal humans, 434
influence of thyrotropic substance on ketone bodies, of, 125
iodine content and menstruation, 706
iodine content of normal and thyrotoxic individuals, 736
iodine content of, in thyroid dysfunction, 303
lipid changes of, during pregnancy, 410
lipids, effect of adrenalin on, 691
lipids, influence of raw pancreas on, 443
lipids and thyroid function, 454
and posterior hypophysis, 432
pressure and adrenal tumors, 572, 692
pressure, effect of exophthalmic goiter and toxic adenoma on, 406
pressure, effect of follicle hormone on, 424
pressure, effect of sodium and potassium salts on, in diabetes mellitus, 731
pressure in hyperthyroidism, 460
pressure and hypophysis, 436, 595, 721
pressure, mechanism of, 243
pressure and thyroid, 458
sodium level in Addison's disease, 115, 874
sugar after acetylcholine, 405
sugar and adrenaline, 402, 575
sugar in diabetes mellitus, 285
sugar in hypoglycemia, 731
sugar and hypophysis, 126, 262
sugar and insulin, 575
sugar and insulin protamine compound, 733
sugar regulation in exercise, 130
BLOOM, C. J. Thyrotoxicosis in children, 453
BLOOMBERG, E. See Albright, F., 133, 447
BLOTNER, H. Blood fat tolerance tests in malnutrition and obesity, 123
BLOUNT, R. F. The influence of additional pituitary anlagen upon the circulatory system of the developing urodele, 430
BLUM, B. B. See Sprague, R. G., 733
BLUMGART, H. L. See Gilligan, D. R., 135
BLUMGART, H. L. See Riseman, J. E. F., 737
BLUMGARTEN, A. S. Treatment of pituitary disorders, 264
BLYTH, J. S. S. See Greenwood, A. W., 417
BODANSKY, M., and V. B. DUFF. Nitrogen and creatine metabolism in relation to environmental temperature and thyroid function, 688
BOGDANOVA, W. See Raspopova, N. A., 737
BOGUE, J. Y., C. L. EVANS, F. GRANDE and F. Y. HSU. The effect of adrenalin and of increased work on the carbohydrate metabolism of the mammalian heart, 403
BOLLER, R., and A. GOEBEL. Clinical aspects and morbid anatomy of pluriglandular sclerosis, 117
BONAR, B. E. Problems of the new-born, 130
BORTZ, E. L. Metabolic stimulants and sodium dinitrophenol, 573
BOUCEK, J. See Bergauer, V., 291
BOURNE, G. See Allen, R., 691
BOWEN, B. D. See Beck, E. C., 442
BOYD, E. M., and M. D. FELLOWS. Blood lipids during pregnancy in guinea pigs, 410
BRAEUCKER, W. Pressoreceptor nervous system and its practical significance in surgery, 603
BRAIER, B., and R. MOREA. Endogenous nitrogenous metabolism in hypophysectomized rats, 430
BRAKEFIELD, J. C. See Abercrombie, W. F., 291
BRAM, I. Graves' disease and pregnancy, 453
BRAM, I. The quinine test for hyperthyroidism, 454
BRAND, E., R. J. BLOCK, M. M. HARRIS and L. E. HINSIE. A convenient method for the preparation of concentrates of follicle stimulating hormone from urine, 430
BRAND, E. See Harris, M. M., 270
BRATTON, A. B., and A. B. FIELD. A case of Simmonds' disease, 264
BRAUN, H. A. See Seevers, M. H., 738
BRAWNER, J. N. See Novak, E., 712
BRAWNER, J. N. See TeLinde, R. W., 424
BREGOU, P. See Durupt, A., 580
BREIPOHL, W. Occurrence of glycogen in endometrial hyperplasia and its significance, 878
BREITMANN, M. J. Contribution to the question of the antithyreoidin dosage, 135
BRENEMAN, W. R. The effect on the chick of some gonadotropic hormones, 430
BRENNER, O., H. DONOVAN and B. L. S. MURTAGH. Total thyroidectomy in the treatment of patients with congestive heart failure and angina pectoris, with note on anaesthetic, 604
BRIDGE, E. M., and H. R. NOLTIE. The action of adrenaline on the respiratory quotient, 403
BRINDEAU, A., H. HINGLAIS and M. HINGLAIS. Studies on physiologic properties of anterior pituitary-like principle, 265
BRITTON, S. W., and R. F. KLINE. Relation of the adrenal cortex to reproduction and lactation, 874
BRONSTEIN, I. P., and G. MILLES. Hypothyroidism and cretinism in childhood. IV. Post mortem report on two cretins, 135
BROUHA, L., and L. DESCLIN. Corpus luteum extracts, 249
BROUHA, L., and L. DESCLIN. Influence of the method used on the results produced in experimental cryptorchidism in rats and guinea pigs, 118
BROUHA, L. Studies on the mobilization of the symphysis pubis in the immature guinea pig, 119
BROUN, D., and A. BEAUNE. Modifications of cardiovascular action of acetylcholine caused by insulin, 729
BROWN-LANGDON, W. Integration of the endocrine system, 405
BRUGER, M. Diabetes mellitus and hyperthyroidism: report of case with fasting blood sugar of 1,500 mg. per hundred cubic centimeters in the absence of coma, 291
BRÜHL, R., and W. RICKOFF. Further studies concerning a rapid test for pregnancy, 411
BUCHANAN, K. S. See Sure, B., 739
BUELL, M. V., and M. B. STRAUSS. Glycogenetic function of the liver in experimental hyperthyroidism, 291
BULBRING, E., and J. H. BURN. The estimation of oestrin and of male hormone in oily solution, 411
BULOW, M. See Plaut, F., 302
BURCH, J. C. See Ellison, E. T., 688
BURDICK, H. O., and G. PINCUS. The effect of oestrin injections upon the developing ova of mice and rabbits, 119
BURFORD, T. H., and A. W. DIDDLE. Effect of total hysterectomy upon the ovary of the Macacus rhesus, 703
BURGDORF, A. L. Systematic studies on the value of the various hypophyseal staining methods with observations on the numerical relationships in the anterior lobe epithelia and their reciprocal relations, 430
BURGESS, W. W. See Marshall, E. K., 127
BURN, J. H. On vaso-dilator fibres in the sympathetic, and on the effect of circulating adrenaline in augmenting the vascular response to sympathetic stimulation, 113
BURN, J. H. See Bulbring, E., 411
BURNS, E. L. See Moskop, M., 258
BURNS, J. H. See Schmidt, E. G., 447
BURNS, R. K., Jr. The transplantation of adult-hypophysis into young salamander larvae, 265
BURROWS, H. Separation of the pubic bones fol-

lowing the administration of oestrogens to male mice, 411
BURROWS, H. Vestigial structures observed in male mice after prolonged treatment with oestrogenic compounds, 411
BUTENANDT, A., and H. DANNENBAUM. On androstenedione, 878
BUTENANDT, A., H. DANNENBAUM, G. HANISCH and H. KUDSZUS. Dehydro-androsterone, 412
BUTENANDT, A., and G. HANISCH. Testosterone, 412
BUTENANDT, A., and H. KUDSZUS. Androstenedione, a potent evocator of male characters, 412
BUTENANDT, A., and K. TSCHERNING. Androsterone, a crystalline male sex hormone. Isolation and purification from male urine, 578
BUTENANDT, A., K. TSCHERNING and G. HANISCH. New members of the male hormone group, 411
BUTENANDT, A. See Allen, W. M., 576
BUTLER, A. M. The dietary management of diabetics at the diabetic clinic of the Infants' and Children's Hospitals, Boston, Mass., 284
BUTLER, M. F. See Chamberlain, C. T., 454
BUTTS, J. S., C. H. CUTLER and H. J. DEUEL. Sexual variation in carbohydrate metabolism; rôle of anterior pituitary in metabolism of diacetic acid, 265
BUXTON, C. L. See Schwartz, H. G., 423
BUXTON, C. L. Transplantation of the hypophysis cerebri to the anterior chamber of the eye in albino rats, 586
BUYSE, A. A case of extreme sex-modification in an adult bovine free-martin, 878
BYTINSKI-SALZ, H. Heteroplastic transplantation of the hypophysis in amblystoma, 431
BYWATER, W. G. See Dox, A. W., 415

Cachexia strumipriva and spontaneous myxedema, 455
CAHANE, M., and T. CAHANE. Certain modifications of the hypophysis after a lesion of the infundibular regulating center of the genital function, 265
CAHANE, T. See Cahane, M., 265
CAHILL, G. F. Air injections to demonstrate the adrenals by x-ray, 403
CAHILL, G. F., R. F. LOEB, R. KURZBROK, A. P. STOUT and F. M. SMITH. Adrenal cortical tumors, 570
Calcium, effect of thyroid, ergosterol and ammonium chloride on excretion of, 736
  excretion due to thyroxin, 302
  in serum, after thyro-parathyroidectomy and parathyroid hormone, 133
CALHOUN, J. A. See Wilkins, W. E., 283
CALLAM, M. Fluorine as specific for parathyroids, 600
Calorigenic action of dinitrophenol after thyroidectomy, 303
  of hypophysis, 282
CAMPBELL, R. E., and F. L. HISAW. The use of corpus luteum in the treatment of dysmenorrhea, 578
Cancer, attempt to retard appearance of, 700
  incidence of mammary gland, and nature of sex cycle in mice, 258
  in mice and thyroid, 300
  presence of 'gonado-stimulin' in urine of patients with, 263
CANNON, W. B., and A. ROSENBLUETH. A comparison of the effects of sympathin and adrenin on the iris, 113
CANTAROW, A. See Haskell, B., 449
Carbohydrate formation and adrenal cortex, 403
  low diet of, in hyperinsulinism, 285
  metabolism, action of parathyroid extract on, 600
  metabolism and autonomic nervous system, 431
  metabolism, effect of sodium and potassium salts on, 731
  metabolism and hypophysis, 431, 721
  metabolism and hypothalamic lesions, 431
  metabolism, sexual variation in, 265
  metabolism, effect of adrenalin on, 114, 403
  metabolism following adrenalectomy, 113
  metabolism, effect of salivary glands on, 130
  metabolism of heart during pancreas diabetes, 445
  metabolism and posterior lobe extract, 726
  metabolism, thyroid gland and, 297
  specific dynamic action of, in hypothyroidism, 298
  tolerance and psychoses, 131
Carcinoma, cervical, and prolan excretion, 125
  experimental and pregnyl, 590
  of thyroid in children, 735
CAREY, H. U., and H. M. HUNT. The chemical nature of cataract in the diabetic, 284
CARIDROIT, P. Summer coloration, castration and moulting in Kaki Campbell ducks, 249
Carotene, effect of, on liver and kidneys, 407
  influence of hyperthyroidism and hypothyroidism on, 451
CARTLAND, G. F., and R. K. MEYER. A study of equilin prepared from pregnant mare urine, 412
CARTLAND, G. F. See Meyer, R. K., 421
CASIDA, L. E. Prepuberal development of the pig ovary and its relation to stimulation with gonadotropic hormones, 412
CASSIDY, M. A. See Kurzrok, R., 418
CASTAGNOU, E. See Aubertin, E., 729
CASTLEMAN, B. See Albright, F., 133
Castration, effect of, on gonadotropic content of hypophysis, 586
  in female and glycogen storage, 712
  and hypophysis, 267, 438
  reaction of hypophysis to estrin injections after, 728
  and replacement therapy, 714
  and vitamin A-deficiency, 257
  and creatin metabolism, 418
CATCHPOLE, H. R., H. H. COLE and P. B. PEARSON. Studies on the rate of disappearance and fate of mare gonadotropic hormone following intravenous injection, 265
CATTELL, R. B. See Perkin, H. J., 459
CAVEET, J. W. Thyroglobulin studies. II The Van Slyke nitrogen distribution and tyrosine and tryptophane analyses for normal and goitrous human thyroglobulin, 734
Cerebro-spinal fluid, fluorine in, 455
  hormones, effect of, on tadpole growth, 700
CHAHOVITCH, X., and K. FRAJND. Contribution to the study of the etiology of goiter, 292
CHAIKOFF, I. L. Survival of two depancreatized dogs treated with insulin, 284
CHAIKOFF, I. L., G. F. HOLTOM and F. L. REICHERT. The glycogen content of liver and muscle in the completely hypophysectomized dog, 431
CHAIKOFF, I. L., and A. KAPLAN. The influence of the ingestion of raw pancreas upon the blood lipids of completely depancreatized dogs maintained with insulin, 443
CHAIKOFF, I. L., L. S. READ and M. E. MATHES. The influence of epinephrine on the blood sugar, lactic acid and inorganic phosphorus of completely hypophysectomized dogs, 123
CHAMORRO, A. Hormonal pregnancy diagnosis with rabbit ovaries autoplastically transplanted into the anterior chamber of the eye, 412
CHAMBERLAIN, C. T., S. JACOBS and M. F. BUTLER. Total blood fat determination as an index of thyroid function, 454
CHAMBERLAIN, D. Hyperchromaffinism, 874
CHARIPPER, H. A. Pregnancy cells in rat pituitary; influence of lipoidal corpus luteum extract, 123
CHARVÁT, J. Treatment of dystrophia adiposogenitalis, 266
CHEN, M. P., L. Y. CH'ENG and R. S. LYMAN. Insulin treatment of drug addiction, 596
CH'ENG, L. Y. See Chen, M. P., 596
CHIDSEY, J. L., and J. A. DYE. The increase in insulin secretion following injection of epinephrine and its relation to the high liver glycogen values obtained, 284
Cholesterol metabolism, present knowledge of, 406
  and pregnancy urine, 273
  and thyrotropic hormone, 278
Cholesterolemia and lutein hormone, 578
  and gonadotropic hormone, 586
Chorioepithelioma, estrin in, 122
  testicular, 251
CHOUKE, K. S., H. FRIEDMAN and L. LOEB. Proliferative activity of the thyroid gland of the female guinea pig during the sexual cycle, 454
CHRISTENSEN, J. T. See Jacobsen, E., 709
CHURCHILL, E. D. See Albright, F., 133
CHUTE, R. The vital importance of the relation of hyperparathyroidism to the formation of certain urinary calculi—and its remedy, 448
CICARDO, V. H. Neuromuscular and reflex excitability of adrenalectomized toads. Mechanism of asthenia, 691
CICARDO-VICENTE, H. Nervous and muscular excitability in hypophysectomized toads. Mechanism of the asthenia, 266
CIOGLIA, L., and D. TORE. Lutein hormone and cholesterolemia, 578
CIOGLIA, L., and D. TORE. Prehypophysial gonadotropic hormone and cholesterolemia, 586
CLAIBORN, T. S. See Macy, J. W., 457
CLARK, B. B., R. B. GIBSON and W. D. PAUL. Increased effectiveness of insulin when given by

injections of doses of equal unitage at intervals of two to four hours, 284
CLARK, B. B., and J. A. GREENE. Effect of low carbohydrate on glucose tolerance in spontaneous hypoglycemia, 285
CLARK, J. H. See Rowntree, L. G., 408
CLARK, J. H. See Rowntree, L. G., 701
CLARK, R. J., J. H. MEANS and H. B. SPRAGUE. Total thyroidectomy for heart disease, 454
CLAUBERG, C. Experimental studies of temporary hormonal sterilization and of prevention of sterility produced by hormones, 413
CLAUBERG, C. Stimulation of the male gonads by female sex hormone, 879
CLAUSEN, F. W. See Freudenberger, C. B., 455
CLAUSEN, V., and M. C. LOTTRUP. Experiences with treatment of diabetes with insulin-epinephrine, 285
CLAY, R. D., and R. D. LAWRENCE. An insulin-resistant diabetic, 285
CLEVELAND, D. See Davis, L., 125
Climacteric, significance and pathogenesis of convulsions during, 257
CLIN, J. See Gildea, E. F., 691
CLONEY, E. See Albright, F., 248
CLOSE, H. G. Basophil adenoma of the pituitary gland with renal changes, 123
COEN, A. See Lévy-Solal, E., 273
COHEN, S. L., and G. F. MARRIAN. Isolation and identification of a combined form of oestriol in human pregnancy urine, 413
COHRS, P. Adhesion of fetal membranes and intersexuality in swine, 119
COLE, H. H., and G. H. HART. Concerning gonadotropic substances in mare serum, 124
COLE, H. H., and R. F. MILLER. Changes in the reproductive organs of the ewe with some data bearing on their control, 413
COLE, H. H. See Catchpole, H. R., 265
COLE, H. H. See Saunders, F. J., 724
COLE, H. H. Two gonadotropic substances in mare serum, 723
COLE, V. V. and G. M. CURTIS. Iodine metabolism of the adult rat in relation to trauma, thyroid activity, and diet, 734
COLLIN, R., and J. DE OLIVEIRA E SILVA. On the direct excretion of the hypophyseal colloid into the pia arachnoid of the hypothalamus in guinea pigs, 266
COLLIN, R., and P. L. DROUET. Action of certain hypophyseal extracts on frog melanophores, 266
COLLIN, R., and P. FLORENTIN. Structure of the hypophysis of the guinea pig post partum, 586
COLLIN, R. and L. HENNEQUIN. Effects of extirpation of the superior cervical ganglion on the pituitary gland in rabbits, 717
COLLINS, C. G., E. P. THOMAS and L. J. MENVILLE. Irradiation of the pituitary gland in the treatment of menopausal symptoms, 431
COLLIP, J. B. Interrelationships among urinary, pituitary and placental gonadotropic factors, 249
COLLIP, J. B., E. M. ANDERSON and D. L. THOMSON. Adrenotropic hormone of anterior pituitary lobe, 124
COLLIP, J. B., L. I. PUGSLEY, H. SELYE and D. L. THOMSON. The mechanism of parathyroid hormone action, 600
COLLIP, J. B. See Bachman, C., 263
COLLIP, J. B. See McEuen, C. S., 711
COLLIP, J. B. See Seyle, H., 261, 281
Comb growth, effect of gonadotropic hormones on, 719
CONE, A. J. See Wenner, W. F., 247
Conditioned reflexes, effect of thyroid on, 735
Congestive heart failure, thyroidectomy in, 736, 737
COOK, F. See Bishop, P. M. F., 703
COOK, J. W., E. C. DODDS and A. W. GREENWOOD. Sex change in the plumage of brown leghorn capons following the injection of certain synthetic oestrus-producing compounds, 250
COOK, J. W., E. C. DODDS, C. L. HEWETT and W. LAWSON. The estrogenic activity of some condensed-ring compounds in relation to their other biological activities, 249
COOK, J. W., E. C. DODDS and F. L. WARREN. Chemistry of oestrogenic substances, 413
COPLAN, H. M., and M. M. SAMPSON. The effects of deficiency of iodine and vitamin A on the thyroid gland of the albino rat, 454
COPPO, M., and M. PISA. Influence of small doses of parathyroid extract on magnesium, 448
COPPOCK, A. See Freed, S. C., 253
CORKILL, A. B. See Hill, R. T., 720
CORNER, G. W. Corpus luteum therapy, 250
CORNER, G. W. See Allen, W. M., 576
CORNIL, L., and J. E. PAILLAS. The hypoglycemic action of testicular extract in cases of diabetes mellitus, 250
Corpus luteum, assay of, 704
and deciduomata, 122
and dysmenorrhea, 578
and endometrium, 254
extracts, effect of, 252
extracts and estrin inhibition, 409
and estrin injections, 716
and folliculin, 122
and glycogen content of liver, 581
hormone of, 580
hormone content of cysts of, 260
hormone formation by placenta, 706, 880
hormone, nomenclature of, 576
hormone, purification of, 252
hormone, standardization and activation of, 252
hormone in urine, 251, 419
and hypophysis, 123
of pseudogestation, 422
substance in treatment of dysmenorrhea, 708
vitamin C concentration in, 410
and uterus, 255, 258, 260
COREY, E. L. Fetal carbohydrate metabolism following adrenalectomy, insulin and glucose experiments on the mother, 113
COSTELLO, R. T. Subclinical adenoma of the pituitary gland, 717
COURRIER, R. A new method of biological assay of extracts of the corpus luteum, 704
COURRIER, R. Studies on the amount of oestrus stimulating material in normal and ectopic testes, 119
COURRIER, R., and G. GROS. Effect of folliculin on the gestating cat, 579
COURRIER, R. and G. GROS. Effect of folliculin on the immature male ape. Action on the accessory sex organs, 414
COURRIER, R., and G. GROS. Endocrinology of pregnancy in the cat, 578
COURRIER, R., and R. RAYNAUD. Experiments on humoral ovarian antagonism effected by the international standard of crystalline folliculin, 250
COURRIER, R., and R. RAYNAUD. Quantitative study on follicular abortion induced in rabbits by crystallized follicular hormone; production of partial abortion, 250
COURVILLE, C. B. See Gunther, L., 269
CRAIG, J., and B. CRAN. Basophil adenoma of the pituitary gland, 266
CRAINICIANU, A. Contribution to the study of arterial hypertension of the menopause, 414
CRAMER, W. and E. S. HORNING. Effect of oestrin on the pituitary gland, 717
CRAMER, W., and E. S. HORNING. Experimental production by oestrin of pituitary tumors with hypopituitarism and of mammary cancer, 579
CRAN, B. See Craig, J., 266
CRANE, W. H. See Abercrombie, W. F., 291
Creatin metabolism, effect of sex hormones on, 418
Creatin metabolism, influence of parathyroid on, 134
Cretin, lingual thyroid gland in, 457
Cretinism and athyreosis, 135
differentiation of, from mongolism, 720
experimental production of, by thyro-cytotoxin, 300
hypophysis in, 283
osseous changes in utero, 135
therapy in, 740
CRILE, G., and G. CRILE, JR. Prevention and treatment of endemic goiter and its complications, 734
CRILE, G., Jr. Preoperative and postoperative treatment of the patient with hyperthyroidism, 734
CROOKE, A. C. and D. S. RUSSELL. The pituitary gland in Addison's disease, 691
CROOKE, A. C. See Hare, D. C., 692
Cryptorchidism, effect of gonadotropic extract in, 727
experimental, 118
treatment of, 708
CULBERTSON, C. G. See Hulpieu, H. R., 590
CURTILLET, A. See Tournade, A., 696
CURTIS, G. M. The iodine relationships of thyroid disease, 604
CURTIS, G. M., L. E. BARRON and F. J. PHILLIPS. Blood iodine studies. V. The blood iodine after total thyroidectomy in man, 734
CURTIS, G. M., and F. J. PHILLIPS. The urinary excretion of iodine. I. The loss of iodine in the urine following thyroidectomy, 292
CURTIS, G. M. See Cole, V. V., 734
CUSHING, H. Hyperactivation of the neurohypophysis as the pathological basis of eclampsia and other hypertensive states, 124
CUSHING, H. See Thompson, K. W., 130

Cushing's disease, 126, 588, 590
Cushing's syndrome with adrenal cortical carcinoma, 692
Gustus, E. L. See Dingle, J. H., 267
Cutler, C. H. See Butts, J. S., 265
Cutler, M., and S. E. Owen. Clinical value of prolan A determinations in teratoma testis, 250
Cuyler, W. K. Extraction of estrin from female urine after acidification with various acids, 251
Cystine, variation of, in inactivated insulin, 730

D'Amour, F. E. See Halpen, S. R., 719
D'Amour, M. C. See Keller, A. D., 590
Dahlberg, G. Follicular hormone and ovulation inhibition, 414
Dahl-Iverson, E. Oestrin treatment of cystic disease of the breast, 879
Dalsace, J. See Lévy-Solal, E., 273
Dambrosi, R. G., L. F. Leloir and A. Novelli. The adrenals and the resynthesis of muscular glycogen after fatigue, 239
Dânes, A. See Langeron, L., 722
Danforth, C. H. and J. K. Fischer. Inability of testicular hormone to masculinize plumage and eye-color of female Brewer's blackbird, 704
Danforth, C. H., and J. B. Price. Failure of theelin and thyroxin to affect plumage and eye-color of the blackbird, 406
Danforth, C. H. Testicular hormones and Sebright plumage, 704
Dannenbaum, H. See Butenandt, A., 412
Dannenberg, A. M., M. A. Bell and B. Gouley. Spontaneous hypoglycemia due to hyperinsulinism in a child, 729
Dantchakoff, V. The inability of male hormone to produce sex reversal in the female genital ridge of chickens and causes for this, 579
Dantchakoff, V. The mechanism of the action of folliculin in the male embryo, 704
Dantchakoff, V. The morphogenic action of folliculin on the testicular ridge in chickens, 579
Das, N., B. N. Ghosh, and B. C. Guha. Electrodialysis of oxytocin, 431
Davis, C. H. Hypothyroidism as a problem in women, 292
Davis, J. E., and A. B. Hastings. Relation of thyroxin to the metabolism of tissues, 292
Davis, J. E., and A. B. Hastings. The effect of thyroxin on the tissue metabolism of excised Limulus heart, 455
Davis, D. See Gilligan, D. R., 135
Davis, L. Effect of hypothalamic lesions and stimulation of the autonomic nervous system on carbohydrate metabolism, 431
Davis, L., D. Cleveland and W. R. Ingram. Carbohydrate metabolism; the effect of hypothalmic lesions and stimulation of the autonomic nervous system, 125
Davis, B. L., Jr. See Luck, J. M., 244
Davis, M. E. The treatment of senile vaginitis with ovarian follicular hormone, 414
Davison, L. W. See Zeckwer, I. T., 283
Davy, L. Factors to be considered in immature female rat titration of pregnancy urine, 267
Deanesly, R., and A. S. Parkes. Comparative activities of compounds of the androsterone-testosterone series, 414
Deanesly, R. and A. S. Parkes. Male hormones and the question of accessory substances, 704
Dechaume, J. See Hermann, H., 571
DeCourcy, J. L. Subtotal bilateral adrenalectomy for hyperadrenalism (essential hypertension), 113
de Fremery, P., S. Kober and M. Tausk. Inhibition of the estrogenic effect of the follicular hormone by progestin, 416
de Jongh, C. L. Cushing's disease, 590
de Mello, R. F. See Martins, T., 275
de Mello, R. F. Oestrus cycles in female rats in parabiosis with males having the internal spermatic artery ligated, 276
Deleonardi, S. Presence of oxytocic, pressor and anti-diuretic factors of the posterior lobe in the cerebrospinal fluid, 586
Del-Pino, M. See Lipschütz, A., 594
Deming, C. L., R. H. Jenkins and G. Van Wagenen. Further studies in the endocrinological relationships of prostatic hypertrophy, 415
Deming, C. L., R. H. Jenkins and G. Van Wagenen. Some endocrinological relationships of prostatic hypertrophy: clinical and experimental studies; preliminary report, 251
deMeio, R. H. See Dill, D. B., 114
Dempsey, E. M., R. Hertz and W. C. Young. The experimental induction of oestrus (sexual receptivity) in the normal and ovariectomized guinea pig, 879
Dennison, M. See Korenchevsky, V., 418, 434, 584, 710, 711
Dennison, M. See Simpson, S. L., 246
de Oliveira e Silva, J. See Collin, R., 266
de Potter, F. The diagnosis of pregnancy by biochemical demonstration of an increase in cholesterol, 278
De Robertis, E. See Rojas, P., 260
Desclin, L. Changes in the hypophysis following castration in the male rat, 267
Desclin, L. Changes in the structure of the anterior lobe of the hypophysis after injections of urine from pregnant women, 267
Desclin, L. Effect of follicular hormone on ovary and anterior hypophysis of the rat, 579
Desclin, L. A note on the production of vaginal mucification in guinea-pigs, 251
Desclin, L. See Brouha, L., 118, 249
DeSef, L. See Hamilton, B., 733
Deuel, H. J. See Butts, J. S., 265
De Wesselow, O. L. V. On the possible rôle of the anterior pituitary in human diabetes, 727
de Winiwarter, H. Effect of incomplete extirpation of the thyroid on the structure of the remaining fragments, 740
de Winiwarter, H. Origin of the thymus and parathyroids in guinea pigs, 453
de Winiwarter, H. Significance of colloid vacuoles of the thyroid, 740
Di Pascal, E. C. Action of alkaline extract of anterior lobe of the hypophysis on the growth and germination of plants, 595
Diabetes insipidus, degeneration of supraoptico-hypophyseal system in, 433
and hypothalamicohypophyseal system, 271, 587
polyuria in, 279
treated with posterior lobe powder intranasally, 437
Diabetes mellitus, abdominal pain in juvenile, 446
and Addison's disease, 694
and adrenals, 698
blood sedimentation rate in, 445
blood sugar in, 285, 286
blood and urine sugar estimations in, 598
calorigenic action of fat and carbohydrate in, 290
capillary and venous blood sugars in, 131
and carbohydrate metabolism of the heart, 445
chemical nature of cataract in, 284
in children, 287
cholesterol metabolism in, 406
and cirrhosis, 447
coma in, 287, 289
complications of, 132
diet in, 284, 285
divided dosage of insulin in, 284
effect of percutaneous insulin in, 446
effect of sodium and potassium salts in, 731
effect of testicular extract on blood sugar in, 250
evaluation of hyperglycemia in treatment of, 289
in hyperthyroidism, 735
and hypophysis, 132, 727
and infantilism, 730
insulin in, 285
insulin-epinephrine treatment of, 285
and insulin protamine compound, 444, 733
insulin-resistance in, 285, 290
insulin requirements in, 288
lipid constituents of nerves in, 599
and mental disorders, 732
following mumps, 290
neuritic manifestations in, 598
new method of treatment of, 598
and obesity, 289, 442
optimum time to administer insulin in, 732
and Paget's disease, 700
and parathyroid extract, 601
and pituitary dwarfism, 730
and pregnancy, 130, 730
and relaxation, 442
retinitis in, 290
rôle of vitamins in, 284
serum lipoids in, 288
social aspects of, 289
specific dynamic action of proteins in, 732
sugar control in, 285
symptoms of, 598
treatment of, 598
visual disturbances in, 446, 598
Diabetic ketosis in juvenile diabetes, 446
di Benedetto, E. Nonexistence of a hypoglycemic action of the blood of hypophysectomized dogs, 264
Dickie, L. F. N. See Thompson, W. O., 282, 305

DIDDLE, A. W. See Allen, E., 576
DIDDLE, A. W. See Burford, T. H., 703
Diet and reproduction, 698
Diiodotyrosine, dangers of, in exophthalmic goiter, 602
in normal and pathological thyroid glands, 734
and iodin elimination, 303
prenatal secretion of, 293
synthesis of active hormone from, 460
DILL, D. B., H. T. EDWARDS and R. H. DEMEIO. Effects of adrenalin injection in moderate work, 114
DILL, D. B., H. T. EDWARDS and S. MEAD. Blood sugar regulation in exercise, 130
DILLON, E. S., and W. W. DYER. Diabetic coma with extreme hyperglycemia, 443
DINGLE, J. H. See Gustus, E. L., 718
DINGEMANSE, E. See Freud, J., 587
DINGLE, J. H., R. K. MEYER and L. E. GUSTUS. Influence of hormones on agglutinin response to B. pertussis in immature rats, 267
Dinitrophenol and heat production, 303
and hypophysis-gonad complex, 456
and obesity, 134
DI PASCAL, E. C. Anterior pituitary extract and germination of seeds, 438
DI PASCAL, E. C. Anterior pituitary extract and plant growth, 277
DIRSCHERL, W., J. KRAUS and H. E. VOSS. New substances affecting the seminal vesicles of the castrate mouse, 879
DOBSZAY, L. v. Further studies on the developmental mechanism of the physiological condition in the genital tract, 579
DODDS, E. C. The hormones and their chemical relations, 415
DODDS, E. C., G. M. HILLS, R. L. NOBLE and P. C. WILLIAMS. Posterior lobe of the pituitary gland: its relationship to the stomach and to the blood picture, 432
DODDS, E. C., and W. LAWSON. Synthetic oestrogenic agents without the phenanthrene nucleus, 880.
DODDS, E. C., R. L. NOBLE and E. R. SMITH. A gastric lesion produced by an extract of the pituitary gland, 125
DODDS, E. C. See Cook, J. W., 249, 250, 413
DOGLIOTTI, G. C. See Bastai, P., 133
DOISY, E. A. See Katzman, P. A., 126, 272
DOISY, E. A. See Wade, N. J., 715
DONNET, V. Folliculin and post-hypophyseal antagonism, 717
DONNET, V. Is there a specific oxytocic substance in the blood of women in labor? 251
DONOVAN, H. See Brenner, O., 604
DORFF, G. B. Sporadic cretinism in one of twins. Report of cases with roentgen demonstration of osseous changes that occurred in utero, 135
DORFMAN, R. I. See Gallagher, T. F., 416
DORMANN, F. See Schroeder, H., 738
DOTTI, L. B. The response of the rabbit to insulin, 443
DOTTI, L. B. See Riddle, O., 280
DOX, A. W., W. G. BYWATER and F. H. TENDICK. A crystalline by-product obtained in the large scale extraction of theelin and theelol, 415
DRESEL, I. The effect of prolactin on the estrus cycle of nonparous mice, 580
DRYFUS, A., and L. P. FERRAZ. Gonads of white mice; injections with trypan blue and urine from pregnant women, 251
DRIESSENS, J. See Lambert, O., 288, 446
DROUET, P. L. See Collin, R., 266
DRUCKREY, H. Effect of hypophyseal hormone content on tumor growth, 586
DRY, T. J. S. See Wagener, H. P., 290
DUFF, V. B. See Bodansky, M., 688
DUNLAP, H. F., and F. P. MOERSCH. Psychic manifestations associated with hyperthyroidism, 292
DUNN, C. W. Use of standardized follicular sex hormone in nervous and mental disorders associated with hypo-ovarian state, 415
DURUPT, A., J. LAGARDE and P. BREGOU. On the presence of a substance antagonistic to estrogenic hormone in the urine of certain women, 580
DU SHANE, G. P., W. T. LEVINE, C. A. PFEIFFER and E. WITSCHI. Experimental constant oestrus and the notion of antigonadotropic hormones, 432
Dwarfism and diabetes mellitus, 730
hypophyseal, 441
DYE, J. A. The exhaustibility of the sympathin stores, 114
DYE, J. A. See Chidsey, J. L., 284
DYER, W. W. See Dillon, E. S., 443
Dysmenorrhea, corpus luteum treatment of, 578
endocrine therapy in, 708
insulin in treatment of, 698
treated with emmenin, 715
use of progestin in, 703
Dystrophia adiposo-genitalis, treatment of, 266

EASTLAND, J. S. See Schmidt, E. G., 447
ECKERT, J. F. See Richter, C. P., 279
EDWARDS, H. T. See Dill, D. B., 114, 130
EGGS, F. Effect of thyrotropic hormone on mineral metabolism, 455
EHRHARDT, C., and H. FISCHER-WASELS. The corpus luteum hormone content of human placenta, 880
EHRHARDT, K., and A. HAGENA. Further researches on corpus luteum hormone, 251
EINHORN, N. H. See Rowntree, L. G., 408, 701
EITEL, H., and A. LOESSER. Control of thyroid activity with animal blood, 604
EITEL, H., and A. LOESSER. Importance of the thyroid for the antithyrotropic action of the blood, 293
EITEL, H., G. LÖHR and A. LOESER. Anterior hypophysis and thyroid gland. The influence of thyrotropic substance upon liver glycogen and blood ketone bodies, 125
ELDEN, C. A., and M. FELLOWS. Relation of potency of anterior pituitary-like hormone to hydrogen ion concentration, 267
ELENEVSKAYA, E. K. See Veber, M. P., 739
ELENEVSKIY, K. F. See Shkurov, B. I., 601
ELLERSIECK, D. See Werner, A. A., 727
ELLISON, E. T., and J. C. BURCH. The effect of estrogenic substances upon the pituitary, adrenals and ovaries, 688
ELLIOTT, P. C. Exophthalmic goiter before one year of age, 293
ELLIS, R. W. B., and W. W. PAYNE. Glycogen disease, 443
ELLISON, E. T. See Mason, K. E., 420
ELLSWORTH, H. C. The action of posterior pituitary hormone upon the blood sugar of the rabbit, 432
ELLSWORTH, H. C. The antagonism between posterior lobe pituitary hormones and insulin, 718
ELLSWORTH, R., and J. E. HOWARD. Studies on physiology of the parathyroid glands, 134
ELLSWORTH, R., and W. H. NICHOLSON. Further observations upon the changes in the electrolytes of the urine following the injection of parathyroid extract, 448
ELLSWORTH, R. See Harrop, G. A., 114
ELMER, A. W. The action of diiodotyrosine and inorganic iodine on the thyroid of guinea pigs receiving injections of anterior lobe hormone (thyrostimulin), 293
ELMER, A. W., G. GIEDOSZ and M. SCHEPS. Action of cortin on thyroid hyperactivity induced in the guinea pig by anterior pituitary thyroid-stimulating substance, 240
ELMER, A. W., B. GIEDOSZ and M. SCHEPS. Effect of vitamins A, C, D on normal and hyperactive thyroids; inhibiting action of vitamins A and C on experimental hyperthyroidism, 604
ELMER, A. W., and M. SCHEPS. Distribution of iodin in the cortical and medullary substance of the adrenal, 240
ELMER, A. W., and M. SCHEPS. Thyroxin and diodotyrosine content of the thyroid of newborn babies and fetuses, 293
ELSOM, K. A., F. C. WOOD and I. S. RAVDIN. Hyperparathyroidism with renal insufficiency, 448
EMERY, F. E., and E. L. SCHWABE. Duration of estrus in ovariectomized and adrenal-ovariectomized rats before and after theelin, 119
Emmenin in treatment of dysmenorrhea, 715
in treatment of menstrual edema, 577
Endocrine activity and blood serum, 701
disorders and behavior problems, 699
gland transplantation and glycemia, 700
glands, effect of cabbage diet on, 699
glands of Frizzle fowl, 576
glands and gastro-intestinal disorders, 702
glands in osteogenesis imperfecta, 118
glands and personality, 406
gland transplants and blood serum, 408
insufficiency and the brain, 304
organ weights and somatological habitus types, 700
studies in infants and children, 574

system, integration of, 405
therapy of benign prostatic hypertrophy, 711
therapy in dysmenorrhea, 708
therapy in mongolian idiots, 408
Endometrium and adrenals, 691
changes following removal of corpora lutea, 254
hyperplasia of, 426, 582, 878
transplants, growth of, 420
ENG, H. Absorption and elimination of folliculin in the human organism. Folliculin content of food, 581
ENG, H. Absorption and elimination of folliculin in the human organism. Studies on the folliculin excretion in urine and feces of normal men, 415
ENGEL, P. Hormone properties of the pineal body, 574
ENGEL, W. J. See Lower, W. E., 420
ENGELHART, E., and O. KIML. Influence of the corpus luteum on the glycogen content of the liver, 581
ENGLE, E. T., and P. E. SMITH. Some uterine effects obtained in female monkeys during continued oestrin administration, with especial reference to the cervix uteri, 415
ENGLISH, H. See Phillips, P. H., 460
ENTWISTLE, R. M., and J. A. HEPP. Testicular chorionepithelioma with gynecomastia and complete pregnancy reactions, 251
Epididymis, adrenal cortical cells in 243
Epilepsy, endocrine therapy in, 118
estrogenic hormone treatment of, 425
Epinephrin and blood sugar, 733
effect of, on fallopian tube, 419
effect of, on sympathectomized human extremity, 115
and hypophysectomy, 123
and insulin secretion, 284
and insulin in treatment of diabetes, 285
and liver glycogen, 284
secretion rate and acetylcholine, 405
in tissue cultures of adrenal glands, 244
EPPINGER, E. C., and W. T. SALTER. The daily requirements in human hypothyroidism of purified, human thyroid hormone at various metabolic levels. A comparison between spontaneous myxedema and cachexia strumipriva, 455
Equilin, activity, analysis and preparation of, 412
ERB, I. H. See Snelling, C. E., 696
ERNSTENE, A. C. The management of complicating factors in hyperthyroidism, 735
ERNSTENE, A. C., J. E. F. RISEMAN and B. STERN. The mechanism of the circulatory changes accompanying insulin hypoglycemia, 597
Erythrocyte counts in menstrual cycle, 702
ESCAMILLA, R. F. Failure of the Reid Hunt acetonitrile reaction as a clinical test for hyperthyroidism, 689
ESCAMILLA, R. F., H. LISSER and H. C. SHEPARDSON. Internal myxedema; report of a case showing ascites, cardiac, intestinal and bladder atony, menorrhagia, secondary anemia and associated carotinemia, 295
ESIASCHWILL, I. N. The influence of sex hormone on the adrenal cortex, 252
ESSEX, H. E. See Steggerda, F. R., 282
Estrin, in chorioepithelioma and hydatidiform mole, 122
colorimetric determination of, 423
effect of continued administration of, on uterus, 415
effect of, upon experimental syphilis, 253
effect of, on hypophysis, 717, 728
effect of, on hypophysis and gonads, 716, 719
effect of, in males, 253, 411, 416, 425, 584
effect of, on pituitary hyperactivity in the menopause, 434
effect of, on uterus, 713
estimation of, in oily solution, 411
inhibition by corpus luteum extracts, 409
injections and abnormalities in newborn rats, 705
injections and development of embryo, 119
procedure for quantitative extraction from urine, 416
production of pituitary tumors and mammary cancer, 579
production of sterility, 713
relation of mechanical cornification to assay of, 707
and response of endometrium to trauma, 423
synergistic with testicular hormones, 418
titration of, in urine, 422
treatment of cystic mastopathia, 879
and uterine epithelium metaplasia, 261
Estrogenic deficiency, syndrome of, 714
gonodotropic substance, 274
hormones, chemical structure of, 415
hormone, effects of, in idiopathic epilepsy and migraine, 425
hormone, effects of large doses of, 257
hormone, effect of, in males, 253
from urine of mares, 878
hormone and human uterine contractions, 581
hormone and mammary cancer in males, 705
and lactation, 880
hormone, substance antagonistic to, 580
synthetic, 880
hormone, therapeutic use of, 121
hormone and thrombo-angiitis obliterans, 421
hormone in treatment of amenorrhea, 418
hormone in treatment of dysmenorrhea, 708
hormone tungstic acid precipitation of, from urine, 415
hormone use of, in male hormone test, 710
Estrone, effect of, on uterus, 711
Estrus, constant and anti-gonadotropic hormone theory, 432
cycle, effect of dinitrophenol and thyroid on, 456
cycle, effect of, on metabolism of hypophysis, 726
cycle, effect of prolactin on, 580
cycle, effect of reduction of ovarian tissue on, 120
cycle, effect of thyroidectomy and thyroid feeding on, 294
cycle, effect of tumor growth on, in normal female rats, 586
cycle, effect of, on tissue metabolism, 715
cycle and mammary gland cancer, 258
cycle and vitamin C in corpus luteum, 410
experimental induction of, 879
-producing compounds, synthetic, 250
in vitamine A deficient rat, 420
ETKIN, W. The phenomena of anuran metamorphosis, The development of the thyroid gland, 604
ETTINGER, G. H., and G. E. HALL. Synergy of adrenalin and acetylcholine on the pulmonary blood-vessels in the rabbit, 403
EUFINGER, H., and J. GOTTLIEB. Action-coefficients of the thyroxin effect in biological experimentation, 294
EVANS, C. L. See Bogue, J. Y., 403
EVANS, E. A., Jr. See Jensen, H., 730
EVANS, G. The adrenal cortex and endogenous carbohydrate formation, 403
EVANS, H. M., and M. E. SIMPSON. Production of superovulation in normal immature rats by injection of the principle in menopause urine, 268
EVANS, H. M., and M. E. SIMPSON. Synergism or augmentation produced by the addition of an hypophyseal synergist to menopause or castration urine, 268
EVANS, L. T. The effect of antuitrin S on the male lizard, Anolis carolinensis, 432
EWING, P. L. The effect of ultraviolet light on some sympathomimetic substances, 240
Exophthalmic goiter and blood pressure, 406
iodin remission in, 295
and pregnancy, 453
recurrent, use of iodin in, 136
and sulphur metabolism, 701
treatment of, 457
Exophthalmos following thyroid extract, 738

FALASCHINI, A., and E. VALLESI. The iodine content of the thyroid in relation to alterations in organs of the genital system in sterile cattle, 605
FALLS, F. H., J. E. LACKNER and L. KROHN. Effect of progestin and estrogenic substance on human uterine contractions: Value of progestin in treatment of habitual and threatened abortion, 581
FALLS, F. H. See Krohn, L., 256
Fat, high diet of, in hyperinsulinism, 285
metabolism hormone, of hypophysis, 716
FAZIKAS, J. F. See Barker, S. B., 698
FAZIKAS, J. F. See Himwich, H. E., 445, 571
FEASTER, J. F., and V. E. NELSON. Diet in relation to reproduction and rearing of young, 698
FECHT, K. E. Treatment of ovarian disturbances with oestruzyl, 252
FELLOWS, M. See Elden, C. A., 267
FELLOWS, M. D. See Boyd, E. M., 410
FELS, E. Biology of the corpus luteum, 252
FELS, E. The corpus luteum hormone—its purification, 252

FELS, E. Standardization and activation of the corpus luteum hormone, 252
FELS, E. Studies on the hormone of the corpus luteum, 580
Female sex hormones, action, nature, assay and interrelations of, 121
effect of, on creatin metabolism, 418
and ocular pressure, 713
FERNANDEZ, R., V. G. FOGLIA, L. F. LELOIR and A. NOVELLI. The adrenal cortex and formation of muscular glycogen at the expense of glucose, 240
FERRANNINI, A. Action of parathyroid extract on carbohydrate metabolism, 600
FERRARI, R. Glutathione in different experimental conditions. Adrenal cortex and glutathione, 240
FERRAZ, L. P. See Dreyfus A., 251
Fertility, periodic, biologic basis of, 580
FEVOLD, H. L., F. L. HISAW and R. GREEP. Effect of oestrin on the activity of the anterior lobe of the pituitary, 433
FEVOLD, H. L. See Leonard, S. L., 273
FIELD, A. B. See Bratton, A. B., 264
FIELDING, U. See Popa, G. T., 278
FIROR, W. M. See Grollman, A., 114, 571
FISHER, A. M. See Scott, D. A. 290
FISHER, C., and W. R. INGRAM. The effect of interruption of the supraoptico-hypophyseal tracts on the antidiuretic, pressor and oxytocic activity of the posterior lobe of the hypophysis, 689
FISHER, C., W. R. INGRAM, W. K. HARE and S. W. RANSON. The degeneration of the supraoptico-hypophyseal system in diabetes insipidus, 433
FISHER, C., W. R. INGRAM and S. W. RANSON. Relation of hypothalamico-hypophyseal system to diabetes insipidus, 587
FISHER, C. See Ingram, W. R., 271
FISHER, J. K. See Danforth, C. H., 704
FISKE, C. H. See Subbarow, Y., 703
FLEISCHMAN, F. See Reiss, M., 302, 723
FLEMING, A. J., and F. C. MACINTOSH. The effect of sympathetic stimulation and of autonomic drugs on the paralytic submixillary gland of the cat, 404
FLORENTIN, P. Excretion of pituitary colloid in the toad. 268
FLORENTIN, P., and D. PICARD. Histological studies of the signs of activity of the endocrine portion of the pancreas, 730
FLORENTIN, P., D. PICARD and M. WEIS. Endocrine changes in the pancreas during gestation, 285
FLORENTIN, P., and M. WEIS. Action of injections of ovalbumin on the hypophysis and thyroid gland of guinea pigs, 268
FLORENTIN, P. See Collin, R., 586
FLOREY, H. W., and H. E. HARDING. The nature of the hormone controlling Brunner's glands, 444
FLUHMANN, C. F. Ovary-stimulating factors and antihormones, 268
Flourine in organic fluids, 605
FOGLIA, V. G. See Fernandez, R., 240
FOLLEY, S. J. Effect of oestrogenic hormones on lactation in the cow, 880
Follicle-stimulating hormone, absence of, in hypophyses of young pigeons, 279
assay of, 122
effect of estrin on, 433
and ovary, 428
Follicular hormone and abortion, 250
absorption and elimination of, 415
action of, on plants, 295
action of, in pregnancy, 424
adrenalin in, 572
and blood pressure, 424
changes in prostate after, 256
crystal form and melting point of, 710
crystalline, standardized, 255
effect of, on egg-production, 426
effect of, on hypophysis, 729
and experimental colloidal goiter, 297
in food, 581
and glycogen storage, 712
inhibitory effect of, 427
and lactation, 577, 723
effect of on males, 120, 414, 416, 593
effect of, on ovaries, 248, 249, 576
and ovulation, 414
and parathyroid insufficiency, 450
and progestin, 416
separation and administration of, 416
and sex reversal in chicks, 579, 704
and skin gland hyperplasia, 260
in treatment of cryptorchidism, 708
and thyroid function, 602
Formalin, effect of, on gonadotropic hormone, 437
FOSS, H. L. The heart in toxic goiter, 735
FOTIN, A. S. See Zaharesco-Karaman, 77, 426
FOWLER, A. F. See Rabinowitch, I. M., 289
FOWLER, J. G. See Beck, E. C. 442
FOWLER, W. M. See Gibson, R. B., 730
FOX, C. A., and R. W. WHITEHEAD. Effect of cortico-adrenal extract on leucocytes in blood in normal adult rabbits, 240
FRANCK, S. Cytologic review of different forms of goiter, compared with clinical cases, 294
FRANCK, S. The physiological histology of the anterior lobe of the hypophysis. Effects of alkaline extracts of anterior lobe on the hypophysis of guinea pigs, 433
FRANCK, S. The physiological histology of the anterior lobe of the hypophysis in normal guinea pigs, 433
FRANCK, S. The physiological histology of the hypophysis in the guinea pig. Secretory cycle and regeneration of the cells, 433
FRANK, R. T. Sex-endocrine factors in blood and urine in health and disease, 253
FRANK, R. T. A suggested test for functional cortical adrenal tumor, 571
FRANK, R. T., and U. J. SALMON. Effect of administration of estrogenic factor upon hypophyseal hyperactivity in the menopause, 434
FRANK, R. T., and U. J. SALMON. Gonadotropic blood and urine cycles in normal menstruating women, 268
FRAJND, K. See Chahovitch, X, 292
FRASER, A. M. See Stehle, R. L., 282
FRAZIER, W. D., and H. FRIEMAN. Alterations in liver glycogen, following thyroid, iodine and glucose feedings, 294
FRAZIER, C. N. See Hu, C. K., 707
FRAZIER, C. N., J. M. MU and C. K. HU. Influence of estrogenic substance upon experimental syphilis of the adult male rabbit, 253
FRAZIER, C. N., and J. W. MU. Development of female characteristics in adult male rabbits following prolonged administration of estrogenic substance, 253
FREED, S. C. Gonadotropic substance in the blood of normal humans, 434
FREED, S. C. Gonadotropic substance in urine of normal children, 434
FREED, S. C., and A. COPPOCK. Gonadotropic substance from teratoma of the testis, 253
FREED, S. C., I. A. MIRSKY and S. SOSKIN. A tungstic acid precipitation method for the extraction of the extrogenic substance from urine, 415
FREEDMAN, B., L. M. WRIGHT and B. WEBSTER. Effect of thyroidectomy and thyroid feeding on the estrus cycle in the rat, 294
FREEMAN, H. E. See Jackson, A. S., 735
FREEMAN, M. See Gulland, J. M., 718
FREEMAN, N. E. See Smithwick, R. H., 115
FREEMAN, W. Personality and the endocrines; a study based upon 1400 quantitative necropsies, 406
FREEMAN, W., and J. M. MELICK. Suprarenal cortex therapy in pernicious vomiting of pregnancy, 240
FREEMAN, W. See Pearl, R., 700
FREUD, J. Demonstration of the difference between "male hormone" extracts from urine and from testicles in hypophysectomized rats, 718
FREUD, J., and E. DINGEMANSE. Differentiation of gonadotropic effects of anterior pituitary extracts, 587
FREUDENBERGER, C. B., and F. W. CLAUSEN. The effect of 1 per cent cod liver oil on the rat, with particular reference to the thyroid gland, 455
FRIBORG, J. N. Friedman's modification of the Aschheim-Zondek test, 268
FRIEDGOOD, H. B. Cyclic response of the thyroid gland to experimental excitation and depression, 294
FRIEDGOOD, H. B. The iodin remission in experimental "exophthalmic goiter" of guinea pigs, 295
FRIEDMAN, B. See Resnik, H., Jr., 302
FRIEDMAN, G. S. See Friedman, M. H., 254
FRIEDMAN, H. See Chouke, K. S., 454
FRIEDMAN, M. H., and G. S. FRIEDMAN. A gonad-stimulating extract from alfalfa, 254
FRIEMAN, H. See Frazier, W. D., 294
FRYSZBERG, A. See Lejwa, A., 419
FUENTE-ALBA, A. See Lipschütz, A., 274

FUERTES, L. B. Treatment of hyperthyroidism with gold salts, 455
FUKUSHIMA, K., and H. KAMEDA. The influence of the urine of pregnancy of the surviving rabbit uterus, 718

GAD-ANDERESEN, K., and E. JARLOV. Biology and technic of the Allen-Doisy test, 582
GAD-ANDERESEN, K., and E. JARLOV. The separation of folliculin and the pharmacological problem associated with it, 416
GAINA, I. See Benetato, G., 570
Galactose metabolism, 408
GALLAGHER, T. F., F. C. KOCH and R. I. DORFMAN. Procedure for quantitative extraction of sex hormones from urine, 416
GALLAGHER, T. F. See Nelson, W. O., 438
GALLOT, G., and G. ROUSSEL. Diagnosis of pregnancy in mares, 582
GARDBERG, M. A review of the present status of the treatment of diabetes mellitus, 285
GARDNER, W. U. Pelvic changes occurring in male mice receiving large amounts of folliculin benzoate, 416
GARDNER, W. U., G. M. SMITH, E. ALLEN and L. C. STRONG. Cancer of the mammary glands induced in male mice receiving estrogenic hormone, 705
GARDNER, W. U., G. M. SMITH and L. C. STRONG. Stimulation of abnormal mammary gland growth by large amounts of estrogenic hormone, 416
GARDNER, W. U., G. M. SMITH, L. C. STRONG and E. ALLEN. Development of sarcoma in male mice receiving estrogenic hormones, 705
GAUNT, J. H. Seen Gaunt, R. C., 404
GAUNT, R., and C. E. TOBIN. Lactation in adrenalectomized rats, 875
GAUNT, R. C., E. TOBIN and J. H. GAUNT. The survival of salt-treated adrenalectomized rats, 404
GEDROYĆ, M. Biological method of obtaining the male hormone (androkinine) from male urine, 254
GEIGER, E. The autonomic innervation of the pancreatic islets, 286
GEIGER, E. Influence of insulin on glycogen content of frog liver, 597
GEILING, E. M. K., and M. R. LEWIS. Further information regarding the melanophore hormone of the hypophysis cerebri, 269
GEILING, E. M. K. See Lewis, M. R., 244
GEIST, S. H. Theca cell tumors, 254
Genital function and lesions of infundibular regulating center, 265
organs and hypophyseal destruction, 436
tract, developmental mechanism of physiological condition in, 579
tract, female and suprarenal cortex, 247
Genotypical basis of sporadic goiter, 296
GERNEZ, L. Medico-legal interest of the diagnosis of pregnancy by hormonal methods. Results of 215 biological reactions, 254
GERNEZ, L. See Marchand-Alphant, A., 274
GERSCHMAN, R., and A. D. MARENZI. Effect of alkaline anterior pituitary extract on minerals of plasma, 587
GERSCHMAN, R., and A. D. MARENZI. Hypocalcemia in pancreatectomized and hypophyso-pancreatectomized dogs, 286
GERSCHMAN, R., and A. D. MARENZI. Hypocalcemia of pancreatectomized dogs, 600
GERSCHMAN, R. See Marenzi, A. D., 127, 594
GERSH, I., and A. D. TARR. The so-called hyaline bodies of herring of the posterior lobe of the hypophysis, 718
GERSTEL, G., and W. NAGEL. Pathological and clinical features of malignant adrenal cortical growth, 404
GERTLER, A. Histidine in human urine, 705
GESCHICKTER, C. F. See Askin, J. A., 570
GESCHICKTER, C. F. See Lewis, D., 584
GESENIUS, H. See Aschheim, S., 577
Gestation, effect of gonadotropic hormones during, 281
endocrine changes in pancreas during, 285
GHOSH, B. N. See Das, N., 431
GIBSON, R. B., and W. M. FOWLER. Infantilism and diabetes mellitus, 730
GIBSON, R. B. See Clark, B. B., 284
GIEDOSZ, B. Effect of thyroid-stimulating hormone on the histological structure of endocrine glands, 605
GIEDOSZ, B. Effect of vitamins A and C on the histological structure of endocrine glands, 574
GIEDOSZ, G. See Elmer, A. W., 240, 604
Gigantism, gonadotropic and sex hormones in urine and saliva in, 441
GILBERT, M. S. The development of the hypophysis: Factors influencing the formation of the pars neuralis in the cat, 269
GILDEA, E. F., and E. B. MAN. The effect of epinephrin of the blood lipoids of normal man, 691
GILLIGAN, D. R., M. C. VOLK, D. DAVIS and H. L. BLUMGART. Therapeutic effect of total ablation of normal thyroid on congestive heart failure and angina pectoris; relationship between serum cholesterol values, basal metabolic rate and clinical aspects of hypothyroidism, 135
GILLIGAN, D. See Riseman, J. E. F., 737
GILLIGAN, D. R. See Stern, B., 129
GILMAN, A., and L. GOODMAN. Effect of pituitrin injection in rabbits on serum osmotic pressure and blood picture, 718
GINESTE, G. See Sabrazès, J., 260
GINGLINGER, A. See Wolff, E., 716
GIROUD, A., and C. P. LEBLOND. Localization of vitamin C in the testis, 254
GIROUD, A., C. P. LEBLOND and R. RATSIMAMANGA. Vitamin C in the different lobes of the hypophysis, 269
GLASER, E., and I. BANNET. Do the salivary glands have an internal secretory effect on the carbohydrate metabolism? 130
GLASER, E., and O. HAEMPEL. The question of the biological basis for the periodic fertility or sterility of women, 580
GLAUBACH, S., and E. P. PICK. Effect of thyroxin on temperature regulation, 605
GLEY, P. The law of the action of the male hormone from the urine, 416
GLEY, P. Masculinizing effect of urine, 254
GLICK, D. See Biskind, G. R., 410
Glucose and adrenals, 240, 572
and sucrose tolerance, comparison of, 447
tolerance studies in Paget's disease, 700
Glutathione and adrenals, 240, 682, 693
in blood after hypophysectomy, 434
in hyper and hypothyroidism, 602
Glycogen concentration and liver amylase, 409
in liver and corpus luteum, 581
Glycemia and endocrine gland transplantation, 700
GNASSI, A. M. Multiple arrhenoblastoma of the ovary, 416
GOADBY, H. K., and R. S. STACEY. On the action of parathormone, 448
GOADBY, H. K., and R. S. STACEY. The action of parathormone, 601
GOEDEL, A. See Boller, R., 117
Goiter, adenomatous, endemic, toxic, 734
blood iodine in, 303
etiology of, 292, 294, 302
experimental colloidal, produced by folliculin, 297
exophthalmic, before one year of age, 293
in hens without gravel, 610
incidence of, in Saskatoon school children, 603
and radioactivity, 608
sporadic, genotypical basis of, 296
treatment of, 609
Goitrogenic diet, effect of, on thyroid in darkness, 299
Gold salts, in treatment of hyperthyroidism, 455
GOLDBERG, L. E., C. L. MINIER and E. L. SMITH. Estrogenic treatment of gonorrheal vaginitis, 119
GOLDBERG, M. M. Acroparesthesia, 417
GOLDBERG, M. M. The treatment of pituitary infantilism with anterior pituitary extracts, 689
GOLDEMBERG, L., and J. SCHRAIBER. Fluorine in blood and cerebro-spinal fluid in pathological states, 455
GOLDEMBERG, L., and J. SCHRAIBER. Method for determination of small quantities of fluorine in human organic fluids, 605
GOLDFARB, W. See Himwich, H. E., 445
GOLDZIEHER, M. A., and H. KOSTER. Adrenal cortical hyperfunction, 404
Gonads, effect of anterior lobe extracts on, 262
effect of estrin on, 719
effects of removal on body growth, 707
effect of urine of pregnancy on, 251
heterosexual transplantation of, 708
and prolonged administration of estrin, 711
secondary sex characters and hypophyseal extract, 590
Gonad-stimulation in parabiotic rats, 421
Gonad-stimulating activity of hypophyses from horses of different ages and sex types, 719
Gonad-stimulating potency of hypophysis, after gonadectomy, 424
Gonadectomy, effect of, on hypophysis, 593

and male hormone preparations, 438
Gonatotropic inhibitory action of monkey sera, 719
substance, assay of, 434
substance, chemical studies of, 437
substance, differentiation of, 588
substance, divided dosages of, 429
substance, effect of, on chick, 430
substance, effect of, in cryptorchidism, 727
substance, effect of, during gestation and lactation, 281
substance, effect of, on follicular development, 724
substance, effect of, on males, 429
substance, effect of, on ovary, 724
substance, effect of reducing agents on, 437
substance, evidence against dual nature of, 437
substance excretion in carcinoma of cervix, 125
substance, method for demonstrating small amounts of, 726
substance from onion, 422
substance from pregnant mare serum, 437, 705
substance and prepuberal development of ovary, 412
substance of pregnancy urine, 272, 708
substance, rate of disappearance of, 265
substances, site of formation of, 439
substance and thyroidectomy, 436
substance, titration of, in urine, 422
substance in treatment of imperfectly migrated testes, 423
substance in treatment of sterility in man, 711
substance, and urinary excretion in mental patients, 270
substance of urine, hypophysis and placenta, 249
substance in urine at menopause, 256, 438
substance and uterus, 258
substance, quantitative determination of small amounts of, 126
GOOCH, M. See Pearl, R., 700
GOODMAN, L., and G. B. WISLOCKI. Cyclical uterine bleeding in a new world monkey (Ateles geoffroyi), 417
GOODMAN, L. See Gilman, A., 718
GOORMAGHTIGH, N., and H. HANDOVSKY. The thyrotropic action of vitamin D., 295
GORDON, M. B. Endocrine studies in infants and children. I. Methods and procedure and diagnostic criteria, 117
GORDON, M. B., and L. KUSKIN. Endocrine studies in infants and children. Time of onset of teething, walking and talking in endocrine disorders: Its relationship to intelligence in endocrine and non-endocrine conditions, 574
GORDON, S., and R. R. GRAHAM. Clinical hyperthyroidism associated with a normal metabolic rate, 606
GORDON, W. H. Fetal hypoglycemia due to hyperinsulinism, 286
GORDON, W. G. See White, A., 135
GOSS, H., and P. W. GREGORY. Glutathione concentration of livers and muscles of rats following injection of hypophyseal growth hormone, 269
GOSSELIN, L. See Mercier, L., 300, 700
GOTTLIEB, J. See Eufinger, H., 294
GOTTLIEB, R. The bitterling test for pregnancy, 880
GOULEY, B. A. Basophilic adenoma of the pituitary; Report of a case of pituitary hypertension, terminating in cerebral apoplexy, 269
GOULEY, B. See Dannenberg, A. M., 729
GRABE, F., O. KRAYER and K. SEELKOPF. Circulatory active substances resembling adrenalin in liver extracts, 575
GRADINESCO, A., N. SANTA and F. LUCAN-JONESCO. Influence of gestation on the survival of adrenalectomized animals, 571
GRAEF, I., J. J. BUNIM and A. ROTTINO. Hirsutism, hypertension and obesity associated with carcinoma of the adrenal cortex, 875
GRAHAM, J. M., and H. L. WALLACE. Toxic goitre: A survey of 125 cases treated surgically, 456
GRAHAM, R. R. See Gordon, S., 606
GRANDE, F. See Bogue, J. Y., 403
Granulosa cell tumors of ovary, 709
in six-year-old girl, 410
GRAVE, B. H., and J. SMITH. Sex inversion in Teredo navalis and its relation to sex ratios, 705
Graves' disease, antithyreoidin in, 135
and endogenous glycine formation, 305
and menstruation, 453
and pregnancy, 453
GRAY, H. See Bayer, L. M., 134
GRAY, J., M. S. KIM and A. C. IVY. Is a portion of the pancreatic secretory response to a meal due to the absorption of digested food products? 877
GREEN, A. See Salter, W. T., 280
GREEN, B. Modern treatment of human infertility, 705
GREEN, W. W., and L. M. WINTERS. Studies on the physiology of reproduction on the sheep; the time of ovulation and rate of sperm travel, 417
GREENE, J. A. See Clark, B. B., 285
GREENGARD, H. See Voegtlin, W. L., 132
GREENWOOD, A. W., and J. S. S. BLYTH. On the relation between the site of injection of androsterone and the comb response in the fowl, 417
GREENWOOD, A. W. See Cook, J. W., 250
GREENWOOD, J., JR. Hypoglycemia as a cause of mental symptoms. Report of cases, 131
GREEP, R. O. See Fevold, H. L., 433
GREEP, R. O. See Lane, C. E., 592
GREEP, R. O. See Stewart, G. E., 441
GREGORY, P. W. See Goss, H., 269
GRÉGOIRE, C. See Grégoire, P. E., 452
GRÉGOIRE, P. E., and C. GRÉGOIRE. Elimination of nucleic acid from the thymus gland after acute involution produced by x-rays, 452
GREGORY, J. A B C of the endocrines, 237
GRIFFITHS, E. P., and L. C. SHRADER. Repeated blood-sugar determinations in certain cases of diabetes, 286
GROLLMAN, A., and W. M. FIROR. The rôle of the hypophysis in experimental chronic adrenal insufficiency, 571
GROLLMAN, A., and W. M. FIROR. Studies on the adrenal. Experimental studies on replacement therapy in adrenal cortical insufficiency, 114
GROS, G. See Courrier, R., 414, 578, 579
GROSS, G. Evolution of the uterine mucosa in the cat, 254
Growth, effect of estrin on, 418
effects of gonadectomy upon, 707
effect of liter-size on, 418
effect of prolactin and thyrotropic substance on, 428
effect of thymus and pineal on, 408
hormone, evidence against individuality of, 428
hormone and glutathione concentration of liver and muscle, 269
hormone, influence of, on bone and kidney, 283
influence of pineal and thymus on, 701
inhibition of, by iodoacetic acid, 693
premature sexual, 417
and thyroid, 733
GRUMBRECHT, P. Elimination of thyrotropic substance in urine of menopausal women, 588
GUELIN-SCHEDRINA, A. Glycogenic function of the liver in chick embryos, 730
GUÉRIN, M. See Oberling, C., 610
GUHA, B. C. See Das, N., 431
GUILLAUMIE, M. See Képinov, L., 272
GUILLIERMOND, A. The action of thyroxin and folliculin on plants, 295
GUINZBOURG, E. Premature sexual development, 417
GULDBERG, E. The site of formation of the sexual hormone in the normal gravid female organism in the light of the hormone analysis of the castrate gravid state, 582
GULLAND, J. M., N. S. LUCAS, M. FREEMAN and S. S. RANDALL. The oxytocic hormone of the posterior lobe of the pituitary gland: ultraviolet absorption spectra, adsorption, and electrodialysis, 718
GÜNTHER, H. Hereditary sexual predisposition to disease, 418
GUNTHER, L., and C. B. COURVILLE. Hypophyseal cachexia (Simmonds' disease) with atrophy of the anterior lobe of the pituitary gland, 269
GUSTUS, E. L., R. K. MEYER and O. R. WOODS. Preparation of the gonadotropic hormone of pregnant mare blood, 705
GUSTUS, E. L., R. K. MEYER and J. H. DINGLE. Relationship of precipitin titers to gonadotropic inhibitory action of monkey sera, 719
GUTIÉRREZ NORIEGA, C., and V. MANRIQUE. Inversion of the action of adrenalin on blood sugar by yohimbin, 875
GUTMAN, A. B., T. L. TYSON and E. B. GUTMAN. Serum calcium, inorganic phosphorus and phosphatase activity in hyperparathyroidism, Paget's disease, multiple myeloma and neoplastic disease of the bones, 601
GUTMAN, E. B. See Gutman, A. B., 601
GUYE, P. See Rutishauser, E., 695
Gynecomastia, causation and treatment of, 408
and testicular chorionepitheliamo, 251

HAARMANN, W. The influence of thyroxin on oxygen consumption of living tissue, 606
HABER, P. See Levaditi, C., 298
HACKFIELD, A. W. The ameliorative effects of therapeutic castration in habitual sex offenders, 254
HAEMPEL, O. See Glaser, E., 580
HAGEDORN, H. C., B. N. JENSEN, N. B. KRARUP and I. WODSTRUP. Protamine insulinate, 444
HAGENA, A. See Ehrhardt, K., 251
HAIN, A. M. Effect upon lactation of oöphorectomy during pregnancy, 705
HAIN, A. M. The effect (a) of litter-size on growth and (b) of oestrone administered during lactation (rat), 418
HAIN, A. M. An effect on the rat of antenatal and postnatal administration of oestrin, 705
HAIN, A. M. The physiology of pregnancy in the rat. Further data bearing on the prolongation of pregnancy with a study of the effects of oöphorectomy during pregnancy, 706
HAINES, S. F. The use of iodine in recurrent exophthalmic goiter, 136
HAINES, S. F., and R. D. MUSSEY. Certain menstrual disturbances associated with low basal metabolic rates without myxedema, 295
HAJAZU, S. See Ito, M., 708, 709
HALES, W. M., G. M. HASLERUD and D. J. INGLE. Time for development of incapacity to work in adrenalectomized rats, 241
HALES, W. M. See Ingle, D. J., 242, 692
HALL, G. E. See Ettinger, G. H., 403
HALPERN, A. C. Cytological responses of rat thyroid to treatment with anterior pituitary and potassium iodide, 296
HALPERN, S. R., and F. E. D'AMOUR. Studies on the gonad-hypophyseal complex in estrin-injected rats, 719
HALPERN, S. R., and I. E. HENDRYSON. Comparative effects of dinitrophenol and thyroid on pituitary-gonadal complex in female rats, 456
HALSTEAD, J. A. Gonadotropic hormone (prolan) in relation to carcinoma of the cervix, 125
HALSTED, J. A. See Albright, F., 248
HAMBLEN, E. C. The endometrium in "endometrial hyperplasia" after therapy, 689
HAMBLEN, E. C. Study of ovaries after administration of a gonadotropic principle of anterior pituitary, 321
HAMBLEN, E. C., and R. A. ROSS. A study of ovaries following preoperative administration of an extract of pregnancy urine, 706
HAMBLEN, E. C., and W. L. THOMAS, JR. Hyperplasia of endometrium: a study of endometrium after treatment, 582
HAMBURGER, C. Gonadotropic hormones of the pregnant mare, 719
HAMBURGER, C. Studies on gonadotropic hormones from the hypophysis and chorionic tissue with special reference to their differences, 588
HAMILTON, B., L. DESEF, W. J. HIGHMAN, JR. and C. SCHWARTZ. Parathyroid hormone in the blood of pregnant women, 733
HAMILTON, B., and W. J. HIGHMAN, JR. A test for abnormally large amounts of parathyroid hormone in the blood, 448
HAMILTON, J. B. Visceral temperatures in the intact and unanaesthetized animal. The uterus of the rat, 689
HAMILTON, R. L., and A. P. KNIGHT. Hypertension simulating thyrotoxicosis, 406
HAMLETT, G. W. The effects of antuitrin S and pituitary extract upon the armadillo ovary, 719
HAMPSON, A. C. See Bishop, P. M. F., 703
HANDOVSKY, H. See Goormaghtigh, N., 295
HANISCH, G. See Butenandt, A., 411, 412
HANSEN, L. P. See McCahey, J. P., 421
HANSEN, I. B. See Leonard, S. L., 436
HANSON, A. M. See Rowntree, L. G., 408, 701
HANUM, S., and J. E. HOLST. Sporadic goiter on genotypical basis, 296
HARA, S. See Takashima, R., 305
HARE, D. C., J. M. ROSS, and A. C. CROOKE. Cortical carcinoma of the suprarenal, with Cushing's basophil pituitary syndrome, 692
HARE, W. K. See Fisher, C., 433
HARDESTY, M. The effect of thyroxin upon the feather of the guinea fowl, 456
HARDING, H. E. See Florey, H. W., 444
HARO, F., and P. P. REGIDOR, 706
HARRIS, L. J., and S. N. RAY. Vitamin C in the suprarenal medulla, 241
HARRIS, M. M., E. BRAND and L. E. HINSIE. Studies of the urinary excretion of gonadal stimulating substance in mental patients, 270
HARRIS, M. M., W. A. HORWITZ and S. E. KATZ. Endocrine studies in mental cases, 575
HARRIS, M. M. See Brand, E., 430
HARRIS, M. M. See Horwitz, W. A., 575
HARRIS, R. E. See Ingle, D. J., 692
HARRIS, S. Neurologic hyperinsulinism, 444
HARRIS, S. See Kraft, R. M., 120
HARROP, G. A., R. ELLSWORTH, L. J. SOFFER, J. H. TRESCHER and A. WEINSTEIN. The mechanism of suprarenal insufficiency in the dog, 114
HARROP, G. A., W. M. NICHOLSON, L. J. SOFFER and M. STRAUSS. Extracellular and intracellular water loss during suprarenal insufficiency in the dog, 241
HART, E. B. See Phillips, P. H., 460
HART, G. H. See Cole, H. H., 124
HARTMAN, F. A., and W. D. POHLE. Extracts containing cortin, 690
HARTMAN, F. A. See Liddell, H. S., 693
HARVEY, A. M. See Marshall, E. K., Jr., 127
HASKELL, B., and A. CANTAROW. Further studies in calcium and parathyroid therapy in chronic ulcerative colitis, 449
HASLERUD, G. M. See Hales, W. M., 241
HASLERUD, G. M. See Ingle, D. J., 242, 692
HASTINGS, A. B. See Davis, J. E., 292, 455
HASTINGS, A. B. See McLean, F. C., 133
HATERIUS, H. O. Oophorectomy and maintenance of pregnancy in the rat, 706
HATERIUS, H. O. Reduction of litter size and maintenance of pregnancy in the oophorectomized rat; evidence concerning the endocrine rôle of the placenta, 706
HAUSCHILD, A. See Kofler, A., 710
HAWKINSON, L. F. Simmonds' disease (pituitary cachexia): Report of case in which the patient responded to anterior pituitary-like principle of pregnancy urine, 270
HAYMAKER, W. See Anderson, E., 262
Heart disease and hyperthyroidism, 306
and thyroidectomy, 454, 603, 604, 736, 737
Heart, effect of adrenalin on carbohydrate metabolism of, 403
and diabetes mellitus, 445
and thyroid feeding, 304
HEIMANN, F., and W. LESCHNITZER. Demonstration and significance of the anterior lobe hormones A and B in 100 individual cases, 706
HELLBAUM, A. A. The gonad stimulating activity of pituitary glands from horses of different ages and sex types, 719
HELLER, R. C. See Soskin, S., 440
Hematopoiesis, effect of thyroidectomy on, 739
HENDERSON, D. N. The treatment of menorrhagia and metrorrhagia by anterior pituitary-like hormone, 255
HENDRYSON, I. E. See Halpern, S. R., 456
HENNEQUIN, L. See Collin, R., 717
HEPP, J. A. See Entwistle, R. M., 251
HERBRAND, W. New test for adrenal cortical hormone and ascorbic acid in guinea pigs poisoned with diphtheria toxin, 405
HERCENBERG, T. See Landau, A., 131
HERMAN, K. Further experience with Simmonds' disease, 270
HERMANN, H., J. DECHAUME and G. MORIN. The adrenin content of the adrenals in dogs after destruction of the dorso-lumbar and sacral segments of the spinal cord, 571
HERMANN, S., and H. KASSOWITZ. Absorption and fate of insulin applied to the living skin, 287
HERMANN, S., and H. KASSOWITZ. Experimental basis for percutaneous insulin effect, 444
Hermaphroditism, hereditary, 259
hormonal, effect of sex hormone on, 584
HEROLD, A. A. Further observations on juvenile diabetics and hyperinsulinism, 287
HEROLD, L. See Anselmino, K. J., 409
HESS, J. H. Blood cholesterol and creatine excretion in the urine as aids to diagnosis and treatment of hypothyroidism, 136
HESS, W. N. Reduction of the islets of Langerhans in the pancreas of fish by means of diet, overeating and lack of exercise, 131
HEUER, G. J., and W. D. ANDRUS. The effect of adrenal cortical extract in controlling shock following the injection of aqueous extracts of closed intestinal loops, 241
HEWETT, C. L. See Cook, J. W., 249
HEYL, J. G. Stability of the thyreotropic substance of the anterior lobe of the hypophysis, 720
HIGGINS, H. L. Two cases of dwarfism, 720
HIGHMAN, W. J., JR. See Hamilton, B., 448, 733
HILL, B. H. The early development of the thyroid gland in amia calva, 456

HILL, H. When is insulin dangerous? 287
HILL, R. T., E. ALLEN and T. C. KRAMER. Cinemicrographic studies of rabbit ovulation, 707
HILL, R. T., A. B. CORKILL and A. S. PARKES. Hypophysectomy of birds. General effects of hypophysectomy of fowls, 720
HILL, R. T., and A. S. PARKES. Hypophysectomy of birds. Effects on gonads, accessory organs and head furnishings, 720
HILLS, G. M. See Dodds, E. C., 432
HIMSWORTH, H. P. Diabetes mellitus. The differentiation into insulin-sensitive and insulin-insensitive types, 597
HIMWICH, H. E., J. F. FAZIKAS, S. B. BARKER and M. H. HURLBURT. The metabolism of tissues excised from adrenalectomized rats, 571
HIMWICH, H. E., W. GOLDFARB and J. F. FAZIKAS. The carbohydrate metabolism of the heart during pancreas diabetes, 445
HIMWICH, H. E. See Barker, S. B., 698
HINGLAIS, H., and M. HINGLAIS. The physiological measure of crystalline folliculin; the relation between the international standard of weight (0.1T) and the Allen Doisy rat unit, 255
HINGLAIS, H. See Brindeau, A., 265
HINGLAIS, M. See Hinglais, H., 255
HINMAN, F., and T. O. POWELL. The gonadotropic hormone in the urine of men with tumor of the testis, 707
HINSEY, J. C. See Markee, J. E., 420, 584
HINSIE, L. E. See Brand, E., 430
HINSIE, L. E. See Harris, M. M., 270
HIRANO, S. See Ogatta, A., 259
HISAW, F. L. The physiology of menstruation in Macacus rhesus monkeys, 582
HISAW, F. L. See Campbell, R. E., 578
HISAW, F. L. See Fevold, H. L., 433
HISAW, F. L. See Leonard, S. L., 273
Histidine in human urine, 705
in pregnancy, 711
HOFFMAN, F., and E. RHODEN. The parathyroid hormone from pregnancy blood, 449
HOFFMAN, M. H. Effect of thyroxin and antithyroid substances on the serum lipase, 296
HOFFMAN, F. See Anselmino, K. J., 262, 409, 577, 716
HOFMANN, A. A case of Cushing's disease with genital bleeding, 720
HOHLWEG, H. Non-operative therapy of Basedow's disease, 456
HOLDEN, R., and E. W. THURSTON. Effects of cattle anterior pituitary extracts and KI on liver glycogen in guinea pigs, 271
HOLMES, M. E. Fatal diabetic coma with acute renal failure, 287
HOLMGREN, H. Variations in blood sugar in animals and the influence of adrenaline and insulin, 575
HOLST, J. E. See Hanum, S., 296
HOLT, H., R. W. KEETON, and B. VENNESLAND. The effect of gonadectomy on body structure and body weight in albino rats, 707
HOLTOM, G. F. See Chaikoff, I. L., 431
Homeostasis, significance of differential depression of vasomotor mechanisms in, 116
Homosexuals, effect of sex hormone on, 584
HOPKINS, M. L. Development of the thyroid gland in the chick embryo, 606
HORA, F. A case of Cushing's syndroma, 588
HOŘEJSI, J. See Jonáš, V., 271
HORGAN, E. See Lyon, J. A., 608
Hormonal sterilization, temporary, 413
Hormone control of estrus, ovulation and mating, 442
controlling fat metabolism, 716
effect of, on uterine activity, 256
follicle-stimulating from urine, 430
formation, site of, in normal, gravid, female organism, 582
gonadotropic, in blood of normal humans, 434
influence of infants' urine, 701
production, species differences in, 232
thyrotropic, source of, 305
regulation of glycogen storage, 712
transmission of, in mother's milk, 457
HORNING, E. S. See Cramer, W., 579
HORNING, E. S. See Cramer, W., 717
HORWITZ, W. A., and M. M. HARRIS. Endocrine therapy in a case of psychic disturbance related to the menstrual cycle, 575
HORWITZ, W. A. See Harris, M. M., 575
HOSEN, H. See Signorelli, J., 305
HOSHIZIMA, T. Effect of bile-acid administration on parathyroid tetany in dogs, 449
HOUGARDY, A. The hypertensive action of adrenin in dogs with lowered blood pressure after adrenalectomy, 242
HOUSSA, P. Action of adrenaline on blood sugar of phlorhizinized animals, 242
HOUSSA, P. See La Barre, J., 243
HOUSSAY, B. A. Effect of hypophysectomy on pregnancy and lactation in the dog, 589
HOUSSAY, B. A. Hyphophysectomy in pregnant and lactating bitches, 720
HOUSSAY, B. A. Lactation induced by anterior hypophyseal extract in male dogs.
HOUSSAY, B. A. Production of lactation in dogs and bitches by anterior pituitary extract, 588
Houssay, B. A. What we have learned from the toad concerning hypophyseal functions, 721
HOUSSAY, B. A., and A. ARTUNDO. Effect of the hypophysis and the thyroid on basal metabolism, 271
HOUSSAY, B. A., A. BIASOTTI and P. MAZZOCCO. The weight of the adrenals in hypophysectomized dogs or those with damaged tuber cinerea, 242
HOUSSAY, B. A., A. BIASOTTI and C. T. RIETTI. Diabetogenic action of anterior pituitary substance under various physiological conditions, 125
HOUSSAY, B. A., A. BIASOTTI and R. SAMMARTINO. Functional modifications of the hypophysis in toads following infundibulo-tubular lesions, 589
HOUSSAY, B. A., A. BIASOTTI and R. SAMMARTINO. Effects of infundibulo-tuberal lesions in the toad, 721
HOUSSAY, B. A., and J. M. LASCANO-GONZALEZ. Hypophysis and compensatory hypertrophy of testes in toads, 271
HOUSSAY, B. A., and J. M. LASCANO-GONZALEZ. The thymus in hypophysectomized dogs, 453
HOUSSAY, B. A., and L. F. LELOIR. Anterior pituitary diabetogenic activity independent of the adrenals, 589
HOUSSAY, B. A., and L. F. LELOIR. Diabetogenic action of anterior hypophysis independent of the suprarenals, 589
HOUSSAY, B. A., and R. SAMMARTINO. Alterations in the parathyroids of pancreatectomized dogs, 601
HOUSSAY, B. A., and R. SAMMARTINO. Anatomical changes in the parathyroids of pancreatectomized dogs, 449
HOUSSAY, B. A., and R. SAMMARTINO. Histological changes in the adrenals of hypophysectomized dogs or those with injured tuber cinerea, 242
HOWARD, C. P., and L. F. Rhea. A case of Simmonds' disease due to a primary tumor of Rathke's Pouch, observed over a period of twelve years, 590
HOWARD, J. E. See Ellsworth, R., 134
HOYLE, C. See Parkinson, J., 301
HRUBETZ, M. C. Pituitary hormones and the blood sugar level, 126
HSU, F. Y. See Bogue, J. Y., 403
HU, C. K. See Frazier, C. N., 253
HU, C. K. and C. N. FRAZIER. Vaginal cornification induced by swabbing and its bearing on the rat unit of estrogenic substance, 707
HUBERMAN, J., and H. H. ISRAELOFF. The application of recent theories in the treatment of undescended testes, 708
HUDSON, H. W. The thymus superstition, 453
HUGH, R. Ovulation in the frog; follicular rupture to fertilization, 422
HUGH, R. Ovulation in the frog; pituitary relations in induced ovulation, 440
HULPIEU, H. R., J. H. WEATHERBY and C. G. CULBERTSON. A comparative study of the Kelly test and the Friedman modification of the Zondek-Aschheim test for pregnancy, 590
HUMMEL, F. C., H. R. STERNBERGER, H. A. HUNSCHER and I. G. MACY. Metabolism of women during the reproductive cycle. Utilization of inorganic elements (a continuous case study of a multipara), 583
HUMPHREY, R. R. Sex reversal in amblystoma; Sex type of gonads developed from gonadic primordia of A. punctatum implanted in axolotl females, 708
HUNSCHER, H. A. See Hummel, F. C., 583
HUNT, H. M. See Carey, H. U., 284
HUNT, H. M. See Hurxthal, L. M., 406
HURLBURT, M. H. See Himwich, H. E., 571
HURXTHAL, L. M. Blood cholesterol and thyroid disease; myxedema and hypercholesteremia, 297
HURXTHAL, L. M., and H. M. HUNT. Clinical relationships of blood cholesterol with a summary of our present knowledge of cholesterol metabolism, 406
HURXTHAL, L. M. See Macy, J. W., 457

HUXLEY, J. S. See Thompson, J. H., 451
Hydatidiform mole, estrin in, 122
Hyperadrenalism, effect of adrenalectomy on, 113
Hypercholesteremia and myxedema, 297
Hypergenitalism, hypophysis and adrenal cortex in, 404
Hyperglycemia and diabetic coma, 443
and posterior hypophysis, 432, 718
Hyperinsulinism and juvenile diabetes, 287
and congenital atresia of pancreatic ducts, 443
in a child, 729
and fetal hypoglycemia, 286
following glucose ingestion, 289
low carbohydrate and high fat diet in, 285
neurologic symptoms in, 444
treatment of, 731
Hyperparathyroidism, serum calcium, inorganic phosphorus and phosphatase activity in, 601
with renal insufficiency, 448
Hypertension, adrenals in, 693
and antidiuretic substance in blood, 436
and basophile cells of hypophysis, 429, 437
and hyperthyroidism, 460
hypophyseal, and cerebral apoplexy, 269
juvenile, 692
relation of diabetes and obesity, 442
simulating thyrotoxicosis, 406
thyrotoxic, 301
Hyperthyroidism, adrenal cortical hormone and nitrogen metabolism in, 115
and arthritis, 459, 735
auricular fibrillation in, 457
basal metabolism and blood cholesterol in, 458
blood iodine in, 459
blood pressure in, 460
clinical, with normal basal metabolic rate, 606
and diabetes mellitus, 291, 606, 735
experimental, effect of sodium fluoride on, 738
experimental, effect of tyrosin in, 453
experimental, glycogenic function of the liver in, 291
experimental, influence of dietary fat on, 457
experimental, influence on storage and conversion of carotene, 451
glutathione in, 602
heart complications in, 735
and hypertension, 460
metabolism in, 453
pregnancy in, 735
psychic manifestations in, 292
psychoneuroses in, 735
quinine test for, 454
treatment of, 455, 734, 735
tuberculosis in, 735
Hypoglycemia, adrenals, liver, hypophysis in, 731
in a child, 729
circulatory changes of, 597
fetal, and hyperinsulinism, 286
and hypophysectomy, 264
and psychoses, 131
Hypo-ovarian state, follicular hormone in, 415
Hypophyseal cachexia, diagnosis of, 276
dwarfism, 441
dysfunction, 264
emaciation, treatment of, by hormone therapy, 439
hormones A and B, demonstration and significance of, 706
hyperactivity of menopause, effect of estrin on, 434
hyperthyroidism, treatment of, 608
Hypophysectomy, action of parathyroid hormone after, 280
and adrenal histology, 242
and adrenal weight, 242
and adrenalin content of adrenals, 242
and adrenotropic principles, 428
and asthenia, 266
in birds, 275, 720
and blood calcium, 286
and carbohydrate metabolism, 123
cardiac function after, 595
and diuresis, 596
and effect of adrenal cortical hormone on resistance, 245
effect of, on basal metabolism, 279
effect of, on mammary gland growth and function, 267
effect of parathyroid extract on bones after, 281
effect of, on red cell response to reduced oxygen tension, 441
and formation of antithyrotropic factor, 594
glucose consumption after, 585
and glucose tolerance, 123, 585
and hypotension after bleeding, 264
and hypoglycemia, 264
and immunization, 280
lactic acid in blood after, 127
and mineral content of plasma, 127
and nitrogen metabolism, 430
pancreatectomy and dextrose tolerance curves in absence of insulin, 440
polydipsia after partial, 279
in pregnant and lactating bitches, 720
and reduced oxygen tension, effect of on blood cells, 441
in tadpole, effect of thyrotropic and adrenotropic hormones after, 122
and thymus, 453
and thyroid regeneration, 298
and thyrotropic principles, 428
and ulceration of digestive tract, 590
Hypophysis, absence of, in case of chondrodystrophie, 439
action of, in parabiosis, 437
in Addison's disease, 691
and adrenal cortex, 271
and adrenal cortical hyperfunction, 404
and adrenal, in relation to endogenous carbohydrate formation, 403
and adrenal insufficiency, 571
adrenotropic hormone of, 124
antagonism of hormones of, 273
anterior lobe extract of, in treatment of cryptorchidism, 708
antidiuretic effect, of posterior lobe extract of, 130
and antithyrotropic substance of blood, 594
assay of gonadotropic hormone of, 128
assay of mammotropic content of, 437
assay of three hormones of, 122
asthenia due to disorder of, 283
basophil adenoma of, 123, 129, 266, 269
basophil cells of, 429
basophil cells in posterior lobe of, in hypertension, 437
and behavior disorders, 699
blood-pressure and uterine-active substance in posterior lobe of, 281
and blood pressure, 436, 595
and blood sugar, 262
and cachexia, 129
calorigenic action of extracts of, 282
and carbohydrate metabolism, 431
and castration, 267
of castrate rats treated with testicular hormones, 418
cell changes in, following injection of thyrotropic hormone, 605
and cerebro-spinal fluid, 700
change in blood chloride due to, 291
changes in, post partum, 586
ciliated cells in, 127
and circulatory system, 430, 457
and compensatory hypertrophy of testes, 271
and Cushing's disease, 126
cytological changes in, with reference to sexual periodicity, 442
cytological response to treatment with anterior lobe of, 296
development of, 269
and diabetes, 727, 730
and diiodotyrosine, 584
differentiation and function of, 427
differentiation of gonadotropic effects of extract of, 587
distribution of vitamine C in, 269
during pregnancy and after parturition, 283
dysfunction from tumor of Rathke's Pouch, 590
and eclampsia, 429
effect of anterior lobe emulsion on resistance of normal and hypophysectomised rats, 438
effect of anterior lobe extract of, on blood sugar, 262
effect of anterior lobe extracts of, on gonads, 262
effect of castration on, 593
effect of corpus luteum extract on, 252
effect of, on endochondral ossification, 281
effect of estrin on activity of, 433
effect of estrin injections on, 716, 717, 719
effect of estrus and spaying on metabolism of, 726
effect of follicular hormone on, 427, 579, 593, 729
effect of gonadotropic content of, on tumor growth, 586
effect of grafts of, 594
effect of hormone of, on bone repair, 440
effect of ovalbumin on, 268
effect of posterior lobe extract on diuresis in pregnancy, 273
effect of posterior extract of, on the fallopian tube, 419
effect of posterior lobe preparation on water interchange, 282

effect of sympathectomy on, 717
effect of thyroidectomy on, 283
effect of vitamins A and C on, 574
elaboration of hormones of, in tissue culture, 262
estrogenic-gonadotropic substance of, 274
and excessive uterine bleeding, 715
excretion of colloid of, 266
extract, administration of, after castration, 117
extract, administration of, after thyroidectomy and adrenalectomy, 117
extract and bile composition, 699
extract and blood sugar level, 126
extract and castration, 438
extract as cause of gastric lesion, 125
extract, diabetogenic action of, 125, 589
extract, effect of, on blood picture, 718
extract, effect of, on islet tissue of pancreas, 284
extract, effect of, on plasma minerals, 587
extract, effect of, on uterine activity, 256
extract and folliculin, 717
extract, and germination of seeds, 438
extract of human, effects of, on guinea pig, 273
extract and lactic acid of blood, 275
extract, masculinizing action of, when combined with folliculin, 421
extract and oxygen consumption, 277
extract and regeneration in axolotls, 264
fat metabolism hormone of, 716
and galactose metabolism, 408
and glutathione of blood, 434
gonadotropic complex of anterior lobe of, 593
gonadotropic hormone content of human anterior lobe, 128
and gonadotropic hormones, 719
and hair growth, 429, 738
heteroplastic transplantation of, 431
histology of, in relation to milk secretion, 435
hormone of, in blood of normal humans, 434
hormone, elimination of, in metropathies of ovarian origin, 278
hormone and salt crystallization patterns, 573
hormone of, in urine of normal children, 434
hyaline bodies of posterior lobe of, 718
and hypertension, 429
and hypoglycemia, 731
implantation, effect of, on agglutinin response to B. pertussis, 267
influence of adrenal cortex on, 404
influence of anterior lobe extract of, on bone repair, 440
influence of light on activity of, 272
influence of light and darkness on vasopressin content of, 721
influence of thyroid and dinitrophenol on histology of, 456
insufficiency of anterior lobe of, and habitual abortion, 435
intermediate lobe of, 280
and ketonuria, 596
lactogenic effect of extract of anterior lobe of, in males, 723
and lesion of infundibular regulating center, 265, 589
and light cycle, 429
and mastitis, 714
and melanophore expansion, 266, 269, 434, 725
metabolic hormone and insulinogenic substance of, 282
in metabolism of diacetic acid, 265
method for quantitating reducing substance of, 280
neurocrine pigmentation of, 440
and nuptial pads of newt, 713
and Paget's disease, 700
and pancreas, 272
physiological histology of anterior lobe of, 433
and pigmentation, 405
and personality, 406
posterior lobe of, and eclampsia, 124
posterior lobe extract of, and hypothyroidism, 129
posterior lobe extract of, and insulin, 718
posterior lobe antagonism, 128
pregnancy cells of, in relation to storage of prolactin and milk secretion, 435
and pregnancy urine hormones, 272
and pregnancy urine injections, 267
pressor and oxytocic hormones of, 282, 595
and prolonged administration of estrin, 711
reaction of, in castrates after estrin injections, 728
reaction of, to prolonged injection of pregnancy urine extracts, 442
relation of acidophiles and basophiles in, 431
relation of anterior and posterior lobes of, to experimental diabetes insipidus, 128
relation of growth factor of, to tumors, 441
secretory cycle of and regeneration of cells, 433
sexual differences of, 424, 439, 594
site of antidiurectic action of extract of, 127
site of influence of secretion of, 435
stability of thyrotropic substance of, 720
staining methods of, 430
and stimulation of testis by artificial light, 429
stimulation of thyroid by, 739
subclinical adenomas of, 717
testis and prostate interrelationship, 420
therapy in mongolian idiots, 408
and thyroid, 294, 301
thyrotropic activity of anterior lobe of, on basal metabolism, 128
thyrotropic content of the human, 276
thyrotropic hormone of, 274, 724
thyrotropic hormone of, and myxedema, 740
of toad, relation of, to skin color, polyuria, and blood pressure, 721
transplantation of, 265, 586
treatment of disorders of, 264
and water metabolism, 277
Hypopituitarism, cholesterol metabolism in, 406
Hypospadias in female rats following estrin injections, 705
Hypothalamic lesions, effect of, on carbohydrate metabolism, 125
somnolence resulting from, 278
Hypothalamico-hypophyseal system and diabetes insipidus, 587
Hypothyroidism, basal metabolism and blood cholesterol in, 458
blood cholesterol and creatine excretion in urine, in, 136
experimental, influence on storage and conversion of carotene, 451
and glutathione in red blood cells, 602
low metabolism in, 457
mild grades of, 304
and posterior pituitary extract, 129
serum cholesterol and basal metabolic rate in, 135
specific dynamic action of carbohydrate and protein in, 298
in women, 292
Hysterectomy, effect of, on life and retrogression of corpora lutea in the rabbit, 419
effect of, on ovary, 703

Ihara, K. Comparative investigation of the testes in different psychoses, 583
Impedance angle and basal metabolism in thyrotoxicosis, 303
Imrie, C. G., and C. N. Jenkinson. The influence of the parathyroid on the metabolism of creatine and phosphoric acid, 134
Inaba, E. Action of acetylcholine on the epinephrine output and blood sugar of dogs, and the splanchnic nerves, 405
Infundibulo-tubular lesions, effects of, 265, 589
Ingle, D. J., W. M. Hales and G. M. Haslerud. Influence of partial adrenalectomy on the work capacity of rats, 242
Ingle, D. J., W. M. Hales and G. M. Haslerud. Work capacity in the rat after destruction of the adrenal medulla, 692
Ingle, D. J., and R. E. Harris. Voluntary activity of the rat after destruction of the adrenal medulla, 692
Ingle, D. J. See Hales, W. M., 241
Ingram, W. R., and C. Fisher. Relation of the hypothalamicohypophyseal system to diabetes insipidus, 271
Ingram, W. R. See Davis, L., 125
Ingram, W. R. See Fisher, C., 433, 587, 689
Inhibin, in prostatic hypertrophy, 711
Innervation and pigment dispersion, 434
of pancreatic islets, 286
Inorganic elements, utilization of, during reproductive cycle, 583
Insanitary condition, effect of, on thyroid gland, 299
Insulin and acetylcholine, 729
action of various reagents on, 730
assay of, 443
augmentation of physiologic response to, 289
and bile composition, 699
and blood sugar, 575
content of islets of pancreas after fasting, 729
dangers of, 287
dextrose tolerance curves in absence of, after hypophysectomy-pancreatectomy, 440
in diabetes mellitus, 285
effect of, on adrenal cortex, 695
effect of, on glycogen content of frog liver, 597
effect of, in liver amylase, 409
effect of zinc salts on action of, 290

enteral absorption of, 731
and epinephrin in treatment of diabetes, 285
and glycolitic system, 447
hypoglucemic action of, and fatty degeneration of liver, 729
increased effectiveness of, in equal frequent dosages, 284
influence of, on Jensen's sarcoma, 288
irradiated, stimulation of adrenal medulla by, 244
-like substance in Barley, 445
mechanism, relation of parathyroids to, 601
and muscular glycolysis, 732
optimum time for administration of, 732
in Paget's disease, 700
percutaneous effects of, 287, 444, 446
and posterior pituitary hormones, 718
-sensitivity and non-sensitivity, 597
sugar utilization after, 131
and sulfur metabolism, 407
therapeutic applications of, 599
treatment of drug addiction, 596
in treatment of dysmenorrhea, 698
protamine compound in diabetes, 444, 733
Insulinogenic substance of hypophysis, 282
Internal secretions and mammary functions, 260
Interstitial cells of testes and prostate size, 424
Iodin, action of, in hyperthyroidism, 453
in adrenals, 240
in adenomatous goiter, 735
blood levels of, in thyroid disorders, 306, 459
content of thyroid and iodin intake, 734
deficiency, effect of, on thyroid, 454
and diet in thyrotoxicosis in children, 453
effect of, on anterior pituitary stimulation of thyroid, 294
effect of excess amounts of, on thyroid, 290
effect of, on hypophysis, 126
effect of, on thyrotropic hormone, 126
elimination of, after diiodotyrosine, 303
metabolism in relation to trauma, thyroid activity and diet, 734
metabolism and thyrotropic hormone, 725
method for determination of, in blood, 299
tolerance test, 736
urinary excretion of, 292
Iodized salt and thyroid surgery, 299
Irradiation of the hypophysis in menopause, 431
Islets of Langerhans, reduction of, by diet, overeating and lack of exercise, 131
ISRAEL, S. L. Evaluation of endocrine therapy in primary dysmenorrhea: analysis of thirty-nine cases, 708
ISRAEL, S. L. See Mazer, C., 257, 690
ISRAELOFF, H. H. See Huberman, J., 708
ITHO, M., and K. TSURIGIRO. Effect of male hormone on the genital organs of young male dogs, 580
ITO, M., S. HAJAZU and F. UENO. The gonadotropic hormone in pregnancy urine, 708
ITO, M., S. HAJAZU and F. UENO. Influence of the gonadotropic hormone of pregnancy urine upon the sexual organs of young bitches and apes, 709
IVANOVA, S. Concerning the mechanism of the action of light on the testis of the bird, 255
IVANOVA, W. See Raspopova, N. A., 737
IVY, A. C. See Morgan, J. E., 300
IVY, A. C. See Atkinson, A. J., 577
IVY, A. C. See Sprague, R., 733
IVY, A. C. See Voegtlin, W. L., 132
IZABOLINSKAYA, R. M. See Leytes, S. M., 699

JACKSON, A. S., and H. E. FREEMAN. Effect of iodine in adenomatous goiter, with especial reference to toxic adenomas, 735
JACOBS, H. R., and A. R. COLWELL. Lesions in the pancreas and in the anterior hypophysis with fatal acidosis following prolonged intravenous administration of glucose (in dogs), 877
JACOBS, S. See Chamberlain, C. T., 454
JACOBSEN, E., and J. T. CHRISTENSEN. Synthetic androsterone: Preliminary experiences with its effect on seminal vesicles in castrated male rats, 709
JACOBSON, B. M. See Subbarow, Y., 703
JARLOV, E. See Gad-Anderesen, K., 416, 582
JEFFERS, K. R. Cytology of the mammary gland of the albino rat, 119
JENKINS, R. H. See Deming, C. L., 251, 415
JENKINSON, C. N. See Imrie, C. G., 134
JENSEN, B. N. See Hagedorn, H. C., 444
JENSEN, H., E. A. EVANS, JR., W. D. PENNINGTON and E. D. SHOCK. The action of various reagents on insulin, 730
JENSEN'S sarcoma, effect of insulin on, 288
JOHN, H. J. Clinical record and postmortem pathology of diabetic children, 287
JOHN, H. J. The diabetic child; etiologic factors, 445
JOHN, H. J. Treatment of diabetic coma, 287
JOHNS, G. A. See Werner, A. A., 727
JOHNSON, C. E. Ovarian response in monkeys (Macacus rhesus) to injections of antuitrin-S, 721
JOHNSTON, J. A. Carbohydrate metabolism. Rôle of the thyroid gland, 297
JONÁŠ, V., and J. HOŘEJŠI. The effect of thyrotropic hormone upon the circulation, 271
JONES, T. Lingual thyroid gland in a cretin of 78 years, 457
JORDAN, W. R., and L. O. RANDALL. Neuropathy in diabetes. Lipid constituents of the nerves correlated with the clinical data, 599
JORDAN, W. R. Neuritic manifestations in diabetes mellitus, 598
JORES, A. Changes of hormonal content of the hypophysis with changes of light and darkness, 721
JORES, A. Hormonal investigations in Cushing's disease, 126
JOSLIN, E. P., and F. H. LAHEY. Diabetes and hyperthyroidism, 606
JOSLIN, E. P., H. F. ROOT, P. WHITE and A. MARBLE. Therapeutic applications of insulin, 599
JULIUS, H. W. Action of gonadotropic extract of urine pregnyl on tar carcinoma, 590

KALK, H. The question of the relation between the anterior hypophysis and the adrenal cortex, 271
KAMEDA, H. See Fukushima, K., 718
KANTER, A. E., C. P. BAUER and A. H. KLAWANS. Hormonal studies with the ovipositor lengthening reaction of the Japanese bitterling, 709
KAPLAN, A. See Chaikoff, I. L., 443
KARDOS, Z. See Simon, A., 281
KARNOSH, L. J., and G. H. WILLIAMS. The psychoses of hypothyroidism and hyperthyroidism, 297
KARNOSH, L. J., and R. E. STOUT. Psychoses of myxedema, 606
KARP, L. The hypophysis in rabbits treated with the hormones recovered from urine of pregnancy, 272
KARP, L., and B. KOSTKIEWICZ. Experimental colloidal goiter produced by folliculin, 297
KASSOWITZ, H. See Hermann, S., 297, 444
KATZ, S. E. See Harris, M. M., 575
KATZMAN, P. A., and E. A. DOISY. A note on the preparation of gonadotropic extracts of urine of pregnancy by tungstic acid precipitation, 272
KATZMAN, P. A., and E. A. DOISY. The quantitative determination of small amounts of gonadotropic material, 126
KAUFMANN, C. Observations of treatment of pruritis, 880.
KAUFMANN, C. Therapeutic uses of ovarian hormones, 880
KAUFMAN, C. The treatment of amenorrhea with large doses of ovarian hormones, 120
KAWAI, H. Relation between hypophysis and various products of internal secretions as reflected on reduced-glutathione contents in blood, 434
KAYSER, F. See Sainton, P., 303
KEESER, E., Thyroid, lipase and catalase, 297
KEETON, R. W. See Holt, H., 707
KEHL, R. Mode of action of mammalian anterior hypophyseal extracts on secondary sexual characteristics of male Discoglossus, 590
KELLER, A. D., and M. C. D'AMOUR. Ulceration of the digestive tract following hypophysectomy, 590
KELLER, T. B. See Zeckwer, I. T., 283
KELLING, D. See Werner, A. A., 727
KENDALL, E. C. Adrenal cortex extract, 572
KENDALL, E. C. See Koelsche, G. A., 115
KENNEDY, R. L. J. Carcinoma of the thyroid gland in children, 735
KENYON, A. T. Thyroid hypertrophy in the rat with reference to the effect of light, 298
KÉPINOV, L., and M. GUILLAUMIE. Inhibitive action exercised by the hypophysis on the endocrine function of the pancreas, 272
KEPLER, E. J. Diseases of the adrenal glands. A review with special reference to the clinical aspects, 242
KEPLER, E. J. See Sprague, R. G., 733

KEPLER, E. J. See Walters, W., 696
Kidney metabolism and the estrual cycle, 715
KIMMEL, L. See Morgan, A. F., 450
KIMURA, G. G. Amount of progestin in corpora lutea of cows, 709
KINGSBURY, B. F. Ultimobranchial body and thyroid gland in the fetal calf, 607
KIRSCH, R. E. See Pincus, G., 713
KITCHEN, H. D. The recognition of myxedema, 607
KIYOHARA, K. Action of secretin on the respiration of tissues of certain organs, 288
KLAFTEN, E. Further contribution to the knowledge of granulosa cell tumors, 709
KLAWANS, A. H. See Kanter, A. E., 709
KLEIN, M. The action of the placenta in the suspension of the oestrous cycle during pregnancy, 709
KLEIN, M., and L. KLEIN. The action of the hormone of the corpus luteum on the uterine mucosa and on the uterine muscles of rabbits is a specific test, 255
KLEINER, I. S., A. I. WEISMAN and D. I. MISHKIND. Use of female bitterling as test for male hormone, 710
KLEINHOLZ, L. H. The melanophore-dispersin principle in the hypophysis of Fundulus heteroclitus, 434
KLEITMAN, N., and S. TITELBAUM. The effect of thyroid administration upon the differentiating ability of dogs, 735
KNAUS, H. Determination of the ovulation and conception period, 255
KNEBEL, R. Contribution to the problem: Lactation theory, 406
KNIGHT, A. P. See Hamilton, R. L., 406
KOBER, S. See de Fremery, P., 416
KOCH, F. C. The biochemistry and physiological significance of the male sex hormone, 583
KOCH, F. C. See Gallagher, T. F., 416
KOCHAKIAN, C. D., and J. R. MURLIN. The effect of male hormone on the protein and energy metabolism of castrate dogs, 710
KODIČEK, E. See Pirchan, A., 701
KOELSCHE, G. A., and E. C. KENDALL. The relation of the suprarenal cortical hormone to nitrogen metabolism in experimental hyperthyroidism, 115
KOENIG, E. C. See Beck, E. C., 442
KOFLER, A., and A. HAUSCHILD. A crystal form and melting-point of the follicular hormone, 710
KOLLER, G., and W. RODEWALD. The influence of light on pituitary activity of the frog, 272
KONSCHEGG, T. Mechanism of blood pressure, 243
KONSULOFF, S. Transmission of hormones in the milk, 457
KORENCHEVSKY, V., and M. DENNISON. The assay of fat-soluble androsterone-diol, 710
KORENCHEVSKY, V., and M. DENNISON. Effect of estrone on normal and castrated male rats, 584
KORENCHEVSKY, V., M. DENNISON and S. L. SIMPSON. Assay of gonadotropic hormone of pregnancy urine on male rats, 434
KORENCHEVSKY, V., M. DENNISON and S. L. SIMPSON. The effects of water-soluble preparations of androsterone and androsterone-diol on castrated rats, 711
KORENCHEVSKY, V., M. DENNISON and S. L. SIMPSON. The prolonged treatment of male and female rats with androsterone and its derivatives, alone or together with oestrone, 418
KORENCHEVSKY, V. See Simpson, S. L., 246
KOSTER, H. See Goldzieher, M. A., 404
KOSTER, L., and P. A. HEERES. Pituitary hyperfunction in tuberculosis, 591
KOSTKIEWICZ, B. See Karp, L., 297
KOTYUKA, E. See Liddell, H. S., 693
KRAFT, R. M., C. S. ROBINSON and S. HARRIS. Effect of Treponema pallidum infection on metabolism of rabbit testis, 120
KRAMER, D. W. Blood sedimentation rate in diabetes mellitus, 445
KRAMER, D. W. Diabetes and pregnancy, 730
KRAMER, T. C. See Hill, R. T., 707
KRARUP, N. B. See Hagedorn, H. C., 444
KRAUL, L. Investigations of the function of the uterine muscle, 256
KRAUS, E. J. By which endocrine processes is the post-partum secretion of milk released? 435
KRAUS, E. J. Cushing's disease, constitutional obesity and suprarenal virilism, 272
KRAYER, O. See Grabe, F., 575
KREMER, D. N. Medullary tumor of the adrenal glands with hypertension and juvenile arteriosclerosis, 692
KRICK, E. T. See Rubin, M. I., 115
KRIEGER, V. I. Histidine in urine as an indication of pregnancy, 711
KROCK, F. See Thompson, E., 726
KROHN, L., F. H. FALLS and J. E. LACKNER. On the use of the lutein hormone, progestin, in threatened and habitual abortion, 256
KROHN, L. See Falls, F. H., 581
KUCHEL, C. C., and M. L. MITCHELL. The effects of stimulation of the adrenal gland upon its content of ascorbic acid, adrenalin and glutathione, 692
KUDSZUS, H. See Butenandt, A., 412
KUHN, R., and H. VETTER. Nicotinic-acid-amide in heart muscle, 407
KUN, H., and O. PECZENIK. The sex-specific effects of the sex hormones on creatine metabolism, 418
KUNKEL, P., and L. LOEB. Effects of human anterior pituitary gland on sex organs and thyroid of the guinea pig, 273
KUNZ, A. C. Anterohypophyseal functional insufficiency as cause of habitual abortion, 435
KURZROK, R., L. WILSON and M. A. CASSIDY. The treatment of amenorrhea with large doses of estrogenic hormone, 418
KURZROK, R. See Cahill, G. F., 570
KURZROK, R. See Wilson, L., 715
KUSCHINSKY, G., and TANG-SÜ. Effect of luteinizing substance on the function of the lipoid containing cells of the ovary, 591
KUSCHINSKY, G., and TANG-SÜ. Effect of luteinizing substance on the testis, 591
KUSCHINSKY, G., and TANG-SÜ. Effect of temperature variations on secretion of thyrotrope hormone, 592
KUSKIN, L. See Gordon, M. B., 574
KYLIN, E. Importance of the hypophysis in blood pressure regulation, 436
KYLIN, E. Secretion of the hypophysis, 435

LA BARRE, J., and P. HOUSSA. Effects of adrenaline on blood sugar of hepatectomized dogs, 243
LA BARRE, J. See Zunz, E., 283, 697
LAANES, T. See Bates, R. W., 428
LABBÉ, H. The vegetable insulinoides and their therapeutic indications, 446
Labor, specific oxytocic substance in blood of women in, 251
LACASSAGNE, A. Action of folliculin on the fecundity of male mice, 120
LACASSAGNE, A. Progressive modifications in the mouse uterus caused by prolonged action of estrone, 711
LACASSAGNE, A. Progressive modifications in the structure of the uterus and tubes of rabbits injected from birth with repeated doses of oestrone, 581
LACASSAGNE, A., and W. NYKA. Accessory corticoadrenal of the epididymis, a constant organ in the rabbit, 243
LACASSAGNE, A., and W. NYKA. Changes in the genital organs of male rabbits following destruction of the hypophysis by radium, 273
LACASSAGNE, A., and W. NYKA. Changes in the genital organs of rabbits following destruction of the hypophysis by radium, 436
LACASSAGNE, A. and W. NYKA. Constant corticoadrenal bodies of the epoöphoron in rabbits, 693
LACASSAGNE, A., and W. NYKA. Effect of removal of the hypophysis on the development of tumors in the rabbit, 592
LACASSAGNE, A., and W. NYKA. Experiments on destruction of the hypophysis of cocks by radium, 436
LACASSAGNE, A., and W. NYKA. The histological changes in a hypophysis destroyed by radium, 273
LACASSAGNE, A., and E. VILLELA. Histologic changes during the epidermoid metaplasia of the posterior prostatic lobes in the male mouse after folliculin, 256
LACKNER, J. E. See Falls, F. H., 581
LACKNER, J. E. See Krohn, L., 256
LACOSTE, A. See Aubertin, E., 729
Lactation, artificially induced, 723
  effect of anterior pituitary extract on, 585, 588, 589
  effect of anti-thyroid protecting substance on, 702
  effect of gonadotropic hormones during, 281
  effect of hypophysectomy on, 276, 589
  effect of oestrone on, 418
  effect of oöphorectomy on, during pregnancy, 705
  influence of Vitamins B and G on, 698
  inhibition of, 409, 577
  physiology of, 577
  and prolan, 585
  prolongation of, 261

resumption of, following child-birth, 406
Lactic acid of blood, effect of adrenalin on, 402
of blood and pituitary extracts, 275
LAGARDE, J. See Durupt, A., 580
LAHEY, F. H. See Joslin, E. P., 606
LAHEY, F. H. See Perkin, H. J., 459
LAHR, E. L. See Bates, R. W., 122, 428
LAHR, E. L. See Riddle, O., 280, 596
LALAND, P. and A. KLEM. Experiments to isolate the antianemic principle of the liver, 877
LALAND, P. See Anker, H., 427
LAMBILLON, J. See Schockaert, J. A., 724
LAMBRET, O., and J. DRIESSENS. Effects of insulin on the evolution of Jensen's sarcoma: opposite effects of small, medium, and large doses, 446
LAMBRET, O., and J. DRIESSENS. Regression and resorption of Jensen's sarcoma under the influence of insulin injected after grafting, 288
LANDAU, A., T. HERCENBERG and I. BEILESS. Contribution to the study of diabetes mellitus based on investigation of capillary and venous blood sugars, 131
LANDAUER, W., and S. B. D. ABERLE. Studies on the endocrine glands of the Frizzle fowl, 576
LANDOWNE, M. Specific dynamic action of carbohydrate and of protein in human hypothyroidism after total ablation of the normal thyroid gland, 298
LANE, C. E., and R. O. GREEP. The follicular apparatus of the ovary of the hypophysectomized immature rat and the effects of hypophyseal gonadotropic hormones on it, 592
LANG, T. Results of fourth series of measurements of connection between radioactivity and goiter, 608
LANGECKER, H. See Schenk, F., 695
LANGERON, L., M. PAGET and A. DÀNES. Action of posterior hypophyseal extract on gastric secretion, 722
LANGERON, L., M. PAGET and J. LEDIEU. Endocrine extracts, blood composition, diuresis and kidney insufficiency, 407
LARRAIN, A. R., R. G. ROBERTS and M. M. KUNDE. Formation of an epinephrin-like substance in autolyzing adrenals glands, 875
LARSON, E. Depressor substances in the posterior lobe of the pituitary, 722
LASCANO-GONZÁLEZ, J. M. Accessory suprarenals in the white rat, 243
LASCANO-GONZÁLEZ, J. M. Pituitary infarcts after producing tuberal lesions in the toad, 592
LASCH, F., and E. SCHÖNBRUNNER. Experimental investigations on the enteral absorption of insulin, 731
LASCANO-GONZÁLEZ, J. M. See Houssay, B. A. 271, 453
LASZT, L., and F. VERZAR. The antagonistic action of vitamin B_9 and adrenal cortical hormone on the inhibitory effects of iodoacetic acid on growth, 693
LASZT, L. See Versar, F., 696
LAURET, G. C. See Lévy-Solal, E., 273
LAWRENCE, C. H. Anterior pituitary-like hormone; clinical study of its effects in acne vulgaris, 593
LAWRENCE, J. H., and H. M. ZIMMERMAN. Pituitary basophilism. Report of a case, 593
LAWRENCE, R. D. See Clay, R. D., 285
LAWSON, W. See Cook, J. W., 249
LEBLOND, C. P. See Giroud, A., 254, 269
LE BRETON, E., and G. SCHAEFFER. Action of thyroxin on the basal metabolism in grown rabbits, 298
LE BRETON, E., and G. SCHAEFFER. Effect of thyroxin on the basal metabolism in growing rabbits, 298
LE CHUITON, F. See Sabrazès, J., 260
LEDIEU, J. See Langeron, L., 407
LEE, R. I., Hypothyroidism: A common symptom, 457
LEITER, S. Ligation of the seminal tract of the rat, 256
LEJEUNE, A. See Schockaert, J. A., 724
LEJWA, A., and A. FRYSZBERG. The value of the Aschheim-Zondek hormone test in diagnosis of pregnancy, 419
LELAND, J. P. See Palmer, W. W., 301
LELKES, Z. Action of human fetal thyroid upon development of frog larvae, 736
LELOIR, L. F. Adrenals and pancreatic diabetes, 698
LELOIR, L. F. See Dambrosi, R. G., 239
LELOIR, L. F. See Fernandez, R., 240
LELOIR, L. F. See Houssay, B. A., 589
LELOIR, L. F., and A. NOVELLI. Titration of the cortical hormone by resistance to morphine, 243
LE MARQUAND, H. S., and D. S. RUSSELL. A case of pubertas praecox (macrogenitosomia praecox) in a boy associated with a tumour in the floor of the third ventricle, 576
LEONARD, S. L., H. L. FEVOLD and F. L. HISAW. Pituitary hormone antagonism, 273
LEONARD, S. L., and T. B. HANSEN. The influence of thyroidectomy on the effectiveness of gonad stimulating hormones, 436
LÉPINE, P., and Z. MÉLAS-JOANNIDÈS. Action of pregnancy urine on blood cholesterol of guinea-pigs, 273
LERICHE, R., and A. JUNG. Changes observed in the parathyroids, thyroid and adrenals following experimental deviation of the bile flow, 878
LERMAN, J. See Salter, W. T., 303, 690
LESCHER, F. G. Comparison of pituitary basophilic syndrome and adrenalcortico-genital syndrome, 243
Leucocytes, effect of cortico-adrenal extract on, 240
LEVADITI, C., and P. HABER. Influence of certain endocrine glands on the receptivity of simians to poliomyelitic virus and on acquired immunity, 298
LEVINE, W. T. See Du Shane, G. P., 432
LEVITT, G. The problem of an antidiuretic substance in the blood of patients with eclampsia and other hypertensive diseases, 436
LÉVY-SOLAL, E., A. COEN and G. C. LAURET. Pregnancy and diuresis in the rabbit. Effect of posterior pituitary extracts, 273
LÉVY-SOLAL, E., P. WALTHER and J. DALSACE. Do pregnancy hormones pass through the placenta, 273
LEWIN, J. See Baudouin, A., 239, 402
LEWIS, D., and C. F. GESCHICKTER. Gynecomestia, virginal hypertrophy and fibroadenomas of the breast, 584
LEWIS, J. T., and F. P. LUDUEÑA. Action of atropin on adrenal secretion produced by splanchnic stimulation, nicotin and quaternary ammoniums, 572
LEWIS, J. T., and E. S. TURCATTI. Pancreatic diabetes in sympathectomized dogs, 288, 731
LEWIS, M. R., and E. M. K. GEILING. Survival and increase of epinephrine in tissue cultures of adrenal glands from chick embryos, 244
LEWIS, M. R. See Geiling, E. M. K., 269
LEYTES, S. M., and R. M. IZABOLINSKAYA. Changes in the composition and secretion of bile during the action of certain internal secretions and vegetative poisons, 699
LI, R. C. The effect of posterior pituitary extract, epinephrine, and acetylcholine on the isolated fallopian tube of the macaque at different stages in the menstrual cycle, 419
LIDDELL, H. S., O. D. ANDERSON, E. KOTYUKA, and F. A. HARTMAN. Effect of extract of adrenal cortex on experimental neurosis in sheep, 693
Light, effect of, on thyroid, 298, 299
and hypophyseal activity, 272
LINDER, G. C. Effect of parathyroid hormone and of tuberculosis on the serum and tissue calcium of guinea-pigs, 449
Lipase, thyroid and, 296, 297
Lipid constituents of nerves in diabetes, 599
in parathyroids, 450
Lipodystrophy, progressive, 701
LIPSCHÜTZ, A. Experiments on the gonadotropic complex of the anterior lobe of the hypophysis, 593
LIPSCHÜTZ, A. On a new gonadotropic factor in the urine of women at the menopause, 256
LIPSCHÜTZ, A., and M. DEL-PINO. Specific sex differences in the anterior lobe of the human hypophysis, 594
LIPSCHÜTZ, H., A. FUENTE-ALBA and T. VIVALDI. Disappearance of prolan from the blood of nephrectomized rabbit, 594
LIPSCHÜTZ, A., A. FUENTE-ALBA and T. VIVALDI. Further notes on the disappearance of prolan injected into rabbits, 274
LIPSCHÜTZ, A., J. MENA and E. VINALS. Ovarian damage and the "law of puberty," 256
LIPSCHÜTZ, A., L. PALACIOS and J. AKEL. Feminization of the male anterior hypophysis in the male rat by injections of folliculin, 593
LIPSCHÜTZ, A., and G. VILLAGRAN. Neutralization of the anterior hypophysis by castration in rats, 593
LIPSCHÜTZ, A., and E. VINALS. Note on an oestrogenetic gonadotropic substance from the anterior

lobe of guinea pig hypophyses, 274
LIPSCHÜTZ, A., and E. VINALS. A note on the mechanism causing the disturbances in the ovary and oestrous cycle following a reduction in the amount of ovarian tissue, 120
LIPSCHÜTZ, A., and T. VIVALDI. On the fats of prolan injected intravenously into rabbits, 274
LIPTCHINA, L. See Zavadovsky, B. M., 426, 728
LISSER, H. Successful removal of adrenal cortical tumor causing sexual precocity in a boy five years of age, 244
LISSER, H. See Escamilla, R. F., 293
LIU, A. C., and A. ROSENBLUETH. Reflex liberation of circulating sympathin, 244
Liver, adrenalin-like substance in extract of, 575
amylase, effect of nutrition and hormones on, 409
antianemic principle of, 877
detoxicating hormone of, 702
essential to adrenalin hyperglycemia, 243
extract, partially purified, use of in anemia, 703
extracts, pigeons as test animals for, 407
function and dextrose tolerance, 440
glycogen, alterations in, 294
glycogen, effect of anterior hypophysis extract and KI upon, 271
glycogen, influence of thyreotropic substance on, 125
glycogenic function of, 730
glycogenic function of, in experimental hyperthyroidism, 291
metabolism and estrual cycle, 715
production of sympathin by, 247
LIVINGOOD, C. S. See Zeckwer, I. T., 283
LOEB, L., and M. G. SMITH. The effect of hysterectomy on the durations of life and retrogression of the corpora lutea and on secondary sex organs in the rabbit, 419
LOEB, L. See Chouke, K. S., 454
LOEB, L. See Kunkel, P., 273
LOEB, L. See Morrin, K. C., 276
LOEB, L. See Moskop, M., 258
LOEB, R. F., D. W. ATCHLEY, and J. STAHL. Rôle of sodium in adrenal insufficiency, 244
LOEB, R. F. See Cahill, G. F., 570
LOEB, R. F. See Stahl, J., 405
LOESER, A. Antithyreotrope factor of the blood and the carbohydrate metabolism of the liver, 594
LOESER, A. Experimental basis for the treatment of menopausal disturbances with diiodotyrosine, 584
LOESER, A. The insulin-sugar treatment of experimental pituitary hyperthyroidism, 608
LOESER, A. Significance of the hypophysis for the formation of the antithyreotrope substance of the blood, 594
LOESER, A. The thyreotropic hormone of the anterior pituitary, 274
LOESER, A. See Eitel, H., 125, 293, 604
LOESER, A. See Muller, R., 276
LOESER, A., and K. W. THOMPSON. The anterior pituitary, iodine and the thyroid gland, 126
LÖHR, G. See Eitel, H., 125
LOEWE, S., and H. E. VOSS. Proof of the occurrence of corpus luteum hormone in the urine of women, 419
LLOYD, V. E. Gonadotropic hormones in the treatment of sterility in man, 711
LONG, C. N. H., and F. D. W. LUKENS. Effect of adrenalectomy and hypophysectomy upon experimental diabetes in the cat, 132
LONG, C. N. H., and F. D. W. LUKENS. Observations on a dog maintained for five weeks without adrenals or pancreas, 132
LONG, C. N. H., and F. D. W. LUKENS. Observations upon hypophysectomized-depancreatized cats, 126
LOPEZ, C. P. Exophthalmic goiter treated with milk of thyroidectomized goats, 457
LOTTRUP, M. C. See Clausen, V., 285
LOUMOS, S. Relation of dietary fats to action of thyroid extract in rats, 457
LOWER, W. E., and D. R. MCCULLAGH. Endocrine therapy of benign prostatic hypertrophy, 711
LOWER, W. E., W. J. ENGEL and D. R. MCCULLAGH. A summary of an experimental research on the control of benign prostatic hypertrophy and a preliminary clinical report, 420
LUCAN-JONESCO, F. See Gradinesco, A., 571
LUCAS, N. S. See Gulland, J. M., 718
LUCK, J. M., L. DAVIS, JR. and W. VAN WINKLE, JR. Effect of administered glucose upon amino nitrogen content of the blood, 244
LUCK, J. M., and G. M. RICHMOND. Stimulation of adrenal medulla by irradiated insulin, 244
LUDUEÑA, F. P. See Lewis, J. T., 572
LUKENS, F. D. W. See Long, C. N. H., 126, 132
LUNDBERG, E. Effect of sex hormone on blood coagulation and its variations in hormonal hermaphrodism and experimental sex changes, 584
LURIE, L. A. Endocrinology and disbehavior disorders of children, 699
Luteinizing hormone, secretion following estrin treatment, 433
LYMAN, R. S. See Chen, M. P., 596
LYON, J. A., and E. Horgan. Dissociation of the thyroid from the sympathetic nervous system and reduction of the blood supply to the thyroid in angina pectoris, 608
LYON, R. M. Insulin requirements of diabetic outpatients, 288
LYONS, W. R., and E. PAGE. Detection of mammotropin in the urine of lactating women, 274

MACCHIARULO, O. The occurrence and rôle of adrenalin in the follicle solution in the ovary, 572
MACFARLANE, C. Dysfunctional uterine bleeding, 699
MACINTOSH, F. C. See Fleming, A. J., 404
MACY, I. G. See Hummel, F. C., 583
MACY, J. W., T. S. CLAIBORN and L. M. HURXTHAL. The circulation rate in relation to metabolism in thyroid and pituitary states (Decholin method), 457
MADHAVA, K. B. See McCarrison, R., 299
MAES, J. General character of the syndrome following adrenalectomy in frogs, 693
MAGDALENA, A. Compensatory hypertrophy of the thyroid in hypophysectomized frogs, 298
MAGEE, H. R., and H. L. SMITH. Auricular fibrillation in hyperthyroidism. The influence of age, 457
MAGISTRIS, H. Antihormonal sterilization of females. Implantation of the male gonads, 257
MAGISTRIS, H. Studies on the anti-hormonal sterilization of females by testicular implantations, 257
Magnesium and parathyroid extract, 448
MAINZER, F. Adrenal syndrome with arterial hypertension, 572
Male gonads, implantation of, in female 257
Male hormones and accessory substances, 704
biochemistry of, 583
comparative activities of natural and synthetic, 414
difference in, 718
effect of, on creatin metabolism, 418
effect of, on genital organs of young male dogs, 580
effect of, on protein and energy metabolism, 710
estimation of, in oily solution, 411
evaluation of, 259
evidence of, in stallion urine, 254
group, new synthetic members, 411
isolation of, 578
physiologic significance of, 583
and scrotal function, 258
and sex reversal in chicks, 579
test, use of female bitterling in, 710
from urine, law of action of, 416
synthetic, 714, 878
Mammary cancer and estrin, 579
cancer in males, influence of estrogenic hormone on, 705
function and internal secretions, 260
gland, abnormal growth of, in male mice produced by folliculin benzoate, 416
gland, cytology of, 119
gland, effect of hypophysectomy on growth and function of, 276
Mammotropin content of pituitaries of thyroidectomized male rats, 437
in urine of lactating women, 274
MAN, E. B., and J. P. PETERS. Serum lipoids in diabetes, 288
MAN, E. B. See Gildea, E. P., 691
MANDELSTAMM, A. Biologic test for the melanophore hormone in pregnancy urine by a fish test, 257
MANN, F. Relation of parathyroids to the insulin mechanism, 601
MANSFELD, G., L. SCHEFFER and F. VON TYUKDY. Relationship between the function and iodine content of the thyroid glands, 608
MARAÑON, G. The significance and pathogenesis of climacteric convulsions, 257
MARAÑON, G., and J. BENITEZ. Cholesterinemia in pathological changes of the cortex, 245
MARBLE, A. See Joslin, E. P., 599
MARBLE, A. Diabetes insipidus treatment with posterior lobe pituitary powder intranasally, 437

MARBLE, A., H. F. ROOT and P. WHITE. Diabetic coma, 289
MARBLE, A. See Root, H. F., 446
MARCANO, A. The posterior-pituitary in hypertension, 437
MARCHAND-ALPHANT, A., and L. GERNEZ. Action of pregnancy urine on the spermatogenesis of rabbits; contribution to the diagnosis of the sex of the fetus, 274
Mare serum, gonadotropic substances in, 124
separation of gonadotropic hormone from, 705
MARENZI, A. D. Action of anterior pituitary lobe extract on blood lactic acid, 722
MARENZI, A. D. The action of extracts of the anterior lobe of the hypophysis on the lactic acid of the blood, 275
MARENZI, A. D. Lactic acid in the blood of hypophysectomized dogs, 127
MARENZI, A. D. Posterior pituitary lobe and blood lactic acid, 275
MARENZI, A. D., and R. GERSCHMAN. The hypophysis and the mineral constituents of the blood, 594
MARENZI, A. D., and R. GERSCHMAN. The mineral substances in the plasma of hypophysectomized dogs, 127
MARENZI, A. D. See Gerschman, R., 286, 587, 600
MARINE, D. Physiology and principal interrelations of the thyroid, 609
MARKEE, J. E., and J. C. HINSEY. Observations on ovulation in the rabbit, 584
MARKEE, J. E., R. A. PASQUALETTI and J. C. HINSEY. Growth of intraocular endometrial transplants in spinal rabbits, 420
MARKEE, J. E., W. M. WELLS and J. C. HINSEY. Studies on uterine growth. A local factor in the rabbit urine, 420
MARRIAN, G. F. See Cohen, S. L., 413
MARSHALL, E. K., Jr., W. W. BURGESS and A. M. HARVEY. The site of the antidiuretic action of pituitary extract, 127
MARTINI, V. Glutathione and adrenals, 693
MARTINS, T. Effects of damage of the testis from ligature of the internal spermatic artery in rats. Destruction of the tabular epithelium, maintenance of the accessory organs, alterations in the accessory organs, alterations in the anterior lobe of the hypophysis, 275
MARTINS, T. Note on the question of "antihormones," 437
MARTINS, T. Precocious development of sex characters in chickens treated with gonad-stimulating substances from the serum of pregnant mares, 275
MARTINS, T. The presence of ciliated cells in the anterior lobe of the hypophysis of the albino rat, 127
MARTINS, T. Technic of hypophysectomy in birds, 275
MARTINS, T., and R. F. DE MELLO. The effect on female rats of parabiotic union with castrated and hypophysectomized males, 275
Masculinization produced by hypophyseal extract combined with folliculin, 421
MASON, K. E., and E. T. ELLISON. The demonstration of oestrus in the vitamin A-deficient rat by supravital study of the vaginal smears, 420
MASON, K. E., and J. M. WOLFE. Relation of castration to vitamin A-deficiency in the rat, 257
MATEER, F. Glands and efficient behavior, 235
MATHIEU, F. Action of follicular hormone on tetany and blood calcium in dogs suffering from chronic parathyroid insufficiency, 450
MATHIEU, F., and B. O. BARNES. The effects of theelin and theelol in latent tetany, 421
MATHES, M. E. See Chaikoff, I. L., 123
MAXWELL, L. C., and F. BISCHOFF. Augmentation of the physiologic response to insulin, 289
MAXWELL, L. C., and F. BISCHOFF. Chemical studies on the pituitary gonadotropic hormone, 437
MAY, R. M. Brephoplastic grafts of hypophysis in the rat, 594
MAYERSON, H. S. The effect of light and of darkness on the thyroid gland of the rat, 299
MAZER, C., D. R. MERANZE and S. L. ISRAEL. Evaluation of constitutional effects of large doses of estrogenic principle, 257
MAZER, C., S. L. ISRAEL and B. J. ALPERS. The time element in the pituitary-ovarian response to large doses of the estrogenic hormone, 690
MAZZOCCO, P. See Houssay, B. A., 242
MCCAHEY, J. F., D. SOLOWAY and L. P. HANSEN. The experimental production of enlargement of the accessory sex organs in the rat, 421
MCCANCE, R. A. Experimental sodium chloride deficiency in man, 694
MCCARRISON, R. The interaction of food and sanitary condition in the causation and prevention of thyroid disease, 136
MCCARRISON, R., and K. B. MADHAVA. The effect of insanitary condition on the thyroid gland and other organs of the body, 299
MCCARRISON, R., and G. SANKARAN. Effect of an exclusive diet of cabbage on the internal organs of rabbits, 699
MCCARRISON, R., and S. SANKARAN. Effect of iodine on growth and metabolism of thyroid tissue, 609
MCCLENDON, J. F. Separation of the "colloid" from living thyroid gland by means of centrifugal force, 458
MCCLURE, R. D. Thyroid surgery and iodized salt, 299
MCCULLAGH, D. R. Studies in blood iodine by the use of a new chemical method, 299
MCCULLAGH, D. R. See Lower, W. E., 420, 711
MCCULLAGH, D. R. See Stimmel, B. F., 725
MCCULLAGH, E. P. Treatment of chronic hypoglycemia, 731
MCEACHERN, D. See Andrus, E. C., 453
MCEUEN, C. S. The growth of the Walker rat tumor in young and old animals, 275
MCEUEN, C. S., H. SELYE and J. B. COLLIP. Some effects of prolonged administration of oestrin in rats, 711
MCGEE, L. C. Blood cholesterol in disturbances of the basal metabolic rate, 458
MCGEE, W. B. The effect of gonadokinetic principle of the pituitary gland and pregnancy urine on conception in the immature albino rat, 595
MCGRATH, E. J. G. Experimental peripheral gangrene. Effect of estrogenic substance and its relation to thrombo-angiitis obliterans, 421
MCKEOWN, T. See Selye, H., 261, 423
MCLEAN, A. J. Pineal teratomas: with report of a case of operative removal, 452
MCLEAN, F. C., B. O. BARNES and A. B. HASTINGS. Influence of thyro-parathyroidectomy and of parathyroid hormone upon state of calcium in serum of the cat, 133
MCLESTER, J. B. Arrhenoblastoma: A special type of teratoma, 712
MCMULLEN, C. J. Complications of diabetes mellitus, 132
MCNIEL, E. E. See Whitehead, R. W., 425
MCQUARRIE, I., W. H. THOMPSON and J. A. ANDERSON. Effects of excessive ingestion of sodium and potassium salts on carbohydrate metabolism and blood pressure in diabetic children, 731
MCQUEEN-WILLIAMS, M. Decreased mammotropin in pituitaries of thyroidectomized male rats, 437
MEAD, S. See Dill, D. B., 130
MEANS, J. H. Therapeutics of the thyroid, 299
MEANS, J. H. Treatment of diseases of the thyroid, 609
MEANS, J. H. See Clark, R. J., 454
MEGAY, L. See Scheffer, L., 303
MÉLAS-JOANNIDÈS, Z. See Lépine, P., 273
Melanophore expansion and hyphophysis, 269, 278, 434, 721, 725,
system, action of adrenalin on, 573
MELICK, J. M. See Freeman, W., 240
MELVILLE, K. I. Pressor and oxytocic fractions of posterior pituitary extract. Comparative effects on blood pressure and intestinal activity, 595
MELVILLE, K. I. See Stehle, R. L., 696
Memorrhagia in Cushing's disease, 720
MENA, J. See Lipschütz, A., 256
Menformone, influence of, on epithelium of neck of the uterus, 425
and ocular pressure, 713
MENNINGER, W. C. The inter-relationships of mental disorders and diabetes mellitus, 732
Menopause, action of ovarian follicular hormone in, 712
and arterial hypertension, 414
elimination of thyrotropic substance in urine of, 588
excretion of gonad-stimulating factor in, after injections of estrin, 434
new gonadotropic factor in urine, at, 256
irradiation of hypophysis and, 431
the thyroid and, 460
urine and superovulation, 268
Menstrual cycle, endocrine therapy in psychic disturbance of, 575
and erythrocyte counts, 702
gonadotropic hormone in relation to, 438
disturbances, functional, treated by x-ray of ovaries

and hypophysis, 715
disturbances, low basal metabolic rates in, 295
edema, treatment of, with emmenin, 577
Menstruation and adrenal cortical hyperfunction, 404
gonadotropic blood and urine cycles in, 268
physiology of, in Macacus rhesus monkeys, 582
progestin in functional disorders of, 703
and thyroid activity, 706
Mental disorders and diabetes mellitus, 732
endocrine studies in, 575
and hypoglycemia, 131
Menville, L. J. See Collins, C. G., 431
Meranze, D. R. See Mazer, C., 257
Mercier, L., and L. Gosselin. Attempt to retard the appearance of cancer, 700
Mercier, L., and L. Gosselin. The thyroid gland of cancerous mice after repeated injections of thyroxin, 300
Mercier, L., and L. Gosselin. The thyroid in a strain of cancerous mice, 300
Merrill, F. See Root, S., 246
Metabolic hormone of hypophysis, 282
Metabolism and circulation rate, 457
effect of thyroxin and vitamin A on, 460
in normal and infected tissue, 120
of splenectomized dogs, 459
vitamin C content of cerebrospinal fluid and adrenals as criterion of increase in, 302
of tissues and thyroxin, 292
Metamorphosis and hypophysis, 721
Metropathies of ovarian origin and anterior pituitary hormone, 278
Meyer, E. A method of purification of gonad stimulating principle from pregnant mare serum, 437
Meyer, O. O. See Stewart, G. E., 441
Meyer, R. K., L. C. Miller and G. F. Cartland. The biological activity of theelol, 421
Meyer, R. K. See Allen, W. M., 409
Meyer, R. K. See Cartland, G. F., 412
Meyer, R. K. See Dingle, J. H., 267
Meyer, R. K. See Gustus, E. L., 705, 719
Mezey, K. See Rothschild, F., 128
Migraine, estrogenic hormone in treatment of, 425
Milcou, St.-M. See Parhon, C. I., 408
Milk, endocrine basis for secretion of, 435
transmission of hormones in, 457
Miles, J. M. See Signorelli, J., 305
Miller, D. S. Effects of thyroxin on plumage of the English sparrow, passer domesticus (Linnaeus), 458
Miller, L. C. See Meyer, R. K., 421
Miller, R. F. See Cole, H. H., 413
Milles, G. See Bronstein, I. P., 135
Minenaga, G. The relation between the thyroid gland and blood pressure, 458
Miner, J. R. See Pearl, R., 700
Mineral metabolism, effect of pituitrin on, 728
and thyrotropic hormone, 455
Minerals of blood, effect of hypophysis on, 594
Minier, C. L. See Goldberg, L. E., 119
Mirsky, I. A. See Freed, S. C., 415
Mirsky, I. A. See Soskin, S., 440
Mishkind, D. I. See Kleiner, I. S., 710
Mislowitzer, E., and L. Stanojević. Contribution to the functional pathology and diagnosis of hypophyseal cachexia, 276
Mitchell, M. L. See Kuchel, C. C., 692
Moehlig, R. C. Paget's disease (osteitis deformans) and osteoporosis. Similarity of the two conditions as shown by familial background and glucose tolerance studies, 706
Moersch, F. P. See Dunlap, H. F., 292
Mollison, A. J. Bipartite ovaries, 712
Mongolism, glandular therapy in, 408
Monobromacetic acid, effect of, on sexual function, 260
Monosodium thyroxin, effect of, 305
Monroe, R. T. Chronic arthritis in hyperthyroidism and myxedema, 459
Moore, C. R. Testicular biology, scrotal function and the male sex hormone, 258
Morales, A. Effects of glucose on metabolism of adrenalectomized dogs, 572
Morales, E. A. Effect of glucose on respiratory metabolism of adrenalectomized dogs, 572
Moran, C. S. See Riddle, O., 279, 280
Morea, R. See Braier, B., 430
Morgan, A. F., I. Kimmel, R. Rhomas and Z. Samisch. The effects of moderate doses of viosterol and of parathyroid extract upon rats, 450
Morgan, J. E., and A. C. Ivy. Experimental production of "cretinism" by thyrocytotoxin, 300
Morgan, J. R. E. The parathyroid glands. A study of the normal gland, 450
Morgan, J. R. E. See Warren, S., 451
Morgan, T. N. Movements of the uterus. The action of extract of corpus luteum on the uterus of the unanesthetized rabbit, 258
Morgan, T. N. Movements of the uterus. The action of the gonadotropic extract on the movements of the uterus of the anesthetized rabbit, 258
Moricard, R. Prolonged action of urine of pregnant women and so-called extracts of the anterior hypophysis of urinary origin followed by loss of receptivity of the rabbit's ovary to these hormal actions, 121
Moricard, R. See Proust, R., 278
Morin, G. See Hermann, H., 571
Morrin, K. C., and L. Loeb. Effect of various anterior pituitary gland preparations on thyroidectomized guinea pigs, 276
Mortimer, H. See Selye, H., 281
Mosenthal, H. O. Hyperglycemia: Evaluation in treatment of diabetes mellitus, 289
Mosinger, M. See Roussy, G., 280, 440
Moskop, M., E. L. Burns, V. Suntzeff and L. Loeb. Incidence of mammary cancer and nature of the sexual cycle in various strains of mice, 258
Mosonyi, J. Effect of thyroid hormone on metabolism of vitamin C., 459
Moszkowska, A. Folliculin as a factor in masculinization, 421
Maszkowska, A. The masculinizing action of extracts of the anterior lobe of the hypophysis on recently castrated male guinea pigs, 438
Mu, J. W. See Frazier, C. N., 253
Muller, E. Quantitative investigations on reflex excitability of normal and hyperthyroid animals, 610
Muller, G. L. Reticulocyte responses in the pigeon produced by material effective and non-effective in pernicious anemia with description of the histologically different reactions of the bone marrow, 407
Müller, J. Hormonal regulation of glycogen storage in the female, 712
Muller, R., H. Eitel and A. Loeser. The thyreotropic content of the human hypophysis, 276
Müllerin duct of male mouse, effect of estrin on, 411
Murlin, J. R. See Kochakian, C. D., 710
Murtagh, B. L. S. See Brenner, O., 604
Muscle glycogen and adrenals, 239, 240
Mussey, R. D. See Haines, S. F., 295
Myocardial degeneration after thyroid feeding, 304
Myxedema and chronic arthritis, 459
internal, 293
psychoses of, 606
recognition of, 607
spontaneous and cachexia strumipriva, 455
treatment of, 609, 740

Nagel, W. See Gerstel, G., 404
Nasal mucous membrane and nasal bones, effect of castration on, 121
Nelson, W. O. The effect of hypophysectomy upon mammary gland development and function in the guinea pig, 276
Nelson, W. O., and T. F. Gallagher. Studies on the anterior hypophysis. The effect of the male hormone preparations upon the anterior hypophyses of gonadectomized male and female rats, 438
Nelson, W. O. See Overholser, M. D., 421
Nelson, V. E. See Feaster, J. F., 698
Nervous and mental disorders, use of follicular sex hormones in, 415
Neuropathy in diabetes, 599
Neustaedter, T. The production of an active endometrium in the human castrate, 258
Newcomb, A. L. Acute abdominal pain in juvenile diabetes mellitus, 446
Nicholson, W. H. See Ellsworth, R., 448
Nicholson, W. M. Observations on the pathological changes in suprarenalectomized dogs, with particular reference to the anterior lobe of the hypophysis, 875
Nicholson, W. M. See Harrop, G. A., 241
Nishikori, S. The relation between the spleen and sulfur metabolism especially the effect of various endocrine glands thereon. The effect of adrenaline on the sulfur metabolism of splenectomized dogs, 407
Nishikori, S. The relation between the spleen and sulfur metabolism especially the effect of various endocrine glands thereon. The effect of insulin and dextrose on the sulfur metabolism, 407

NISHIKORI, S. The relation between the spleen and sulfur metabolism especially the effect of various endocrine glands thereon. The effect of removal of the spleen upon the sulfur metabolism, 407
NISHIKORI, S. The relation between the spleen and sulfur metabolism especially the effect of various endocrine glands thereon. The effect of thyroid gland on the sulfur metabolism of splenectomized dogs, 459
Nitrogen metabolism and adrenalectomy, 695
relation of adrenal cortical hormone to, 115
Nitrous acid, effect of, on gonadotropic hormone, 437
NOBLE, R. L. See Dodds, E. C., 125, 432
NOLTIE, H. R. See Bridge, E. M., 403
NONIDEZ, J. F. Innervation of the thyroid gland; distribution and termination of the nerve fibers in the dog, 459
NOVAK, E. Glandular physiology and therapy; therapeutic use of estrogenic substances, 121
NOVAK, E. Some newer aspects of reproductive physiology, 258
NOVAK, E., and J. N. BRAWNER. Granulosa cell tumors of the ovary, 712
NOVELLI, A. See Dambrosi, R. G., 239
NOVELLI, A. See Fernandez, R., 240
NOVELLI, A. See Leloir, L. F., 243
NYKA, W. See Lacassagne, A., 243, 273, 436, 592, 693

OBERLING, C., and M. GUERIN. Thyroid hyperplasia and goiter in hens kept in cages without gravel, 610
Obesity and adrenal cortical hyperfunction, 404
constitutional, adrenal virilism and Cushing's disease, 272
relation of diabetes and hypertension to, 442
and sugar tolerance, 289
OCAÑA, T. Histological study of tissues of animals treated with large doses of carotene, lipids of carrots and a concentrate of vitamin A, 407
OEHME, C., H. PAAL and H. O. KLEINE. The action of thyreotropic hormone and the Reid-Hunt test, 276
Oestriol, isoluation of combined form from urine, 413
Oestrone administration and separation of pubic bones, 411
effects of, growth and lactation, 418
effect of, on uterus and tubes of rabbits, 581
Oestruzyl, treatment of ovarian disturbances with, 252
O'FARRELL, J. M. Hereditary hermaphroditism, 259
OGATA, A., S. HIRANO and S. TANAKA. Studies on male sex hormone. Evaluation of male sex hormone by the cock-comb method, 259
OGILVIE, R. F. Sugar tolerance in obese subjects. A review of sixty-five cases, 289
OKKELS, H. Cellular structure and cellular activity. With contributions to dynamic cytology of kidney and thyroid gland, 610
OLDHAM, F. K. See Stehle, R. L., 696
OLMER, D., J. OLMER, J. PAILLAS and J. VAGUE. Local in vivo glycemia following intravenous injections of insulin, 732
OLMER, J., J. E. PAILLAS and B. SICNASI. Effect of parathyroid extract on the glycemia in diabetics, 601
OLMER, J. See Olmer, D., 732
OPRISIU, C. See Benetato, G., 570
ORÍAS, O. Cardiac function of hypophysectomized toads, 595
ORÍAS, O. Pituitary and blood pressure in toads, 595
ORNSTEIN, I. See Parhon, C. I., 450, 736
Osseous changes in utero in cretinism, 135
Ossification, endochondral, effect of anterior hypophysis on, 281
Osteitis fibrosa cystica and ovariectomy, 450
OSTERBERG, A. E. See Sprague, R. G., 733
OSTERREICHER, W. Gonadotropic hormone of the hypophysis and the menstrual cycle, 438
Ovalbumin, effect of, on thyroid and hypophysis, 268
Ovarian dysfunction, studies on, 248
follicular hormone in senile vaginitis, 414
function and sugar tolerance, 289
hormones in treatment of amenorrhea, 120
insufficiency, local hormone therapy in, 261
tissue, effect of reduction of, on ovary and estrus cycle, 120
Ovariectomy and blood calcium, 450
cornification after, 716
and duration of estrus after theelin, 119
during pregnancy, effect of, on endometrium, 254
effect of, on growth and body weight, 707
maintenance of pregnancy after, in rat, 706
production of active endometrium after, 258
Ovary and adrenals, 691
and adrenal cortical hyperfunction, 404
after hypophysectomy, 592
antagonism to thyroid, 736
bipartite, 712
carcinoma of, in six-year-old girl, 410
corpus luteum cysts of, 260
cystic degeneration of, in Cushing's disease, 720
deficiency and galactose metabolism, 408
effect of follicular hormone on, 579
effect of gonadotropic hormones on, 719, 724
effect of ovarian follicular hormone on, 576
effect of pregnancy urine extract on, 706
effect of testicular implants on, in young rats, 432
effect of total hysterectomy on, 703
Ovary, effect of tumor growth on, in normal rat, 586
effect of vitamins A and C on, 574
and oestrin injections, 716
extract and erythrophore expansion, 409
and follicle-stimulating hormone, 428
Golgi apparatus of follicle cells during secretion and vitelogenesis, 260
granulosa cell tumors of, 712
hormones and mastites, 714
hormone in menopause, 712
therapeutic uses of, 880
irradiation, excretion of theelin after, 423
multiple arrhenoblastoma of, 416
prepuberal development of, 412
response to androsterone, 417
response to estrin, 433
stimulation of, by extracts of urine from normal children, 434
transplantation in pregnancy test, 412
OVERHOLSER, M. D., and W. O. NELSON. The effect of estrin and male hormone injected separately and simultaneously upon the smooth muscle and epithelium of the seminal vesicle in the albino rat, 421
Ovulation, cinemicrographic studies of, 707
induced by pituitary hormone, 439, 440
inhibition and follicular hormone, 414
in the rabbit, 584
OWEN, S. E. The biologic diagnosis of teratoma testis, 259
OWEN, S. E. See Culter, M., 250
Oxidizing agents, effect of, on gonadotropic hormone, 437
Oxygen consumption and anterior pituitary hormone, 277
and thyrotropic hormone, 724
of tissue, influence of thyroxin on, 606
Oxytocic factor in cerebrospinal fluid, 586
hormone of hypophysis, 718
and pressor hormones, purification and chemistry of, 282
Oxytocin, electrodialysis of, 431

PAAL, H. Concerning the hormonal influence upon the metabolism of surviving thyroid tissue, 300
PAAL, H. Thyroid and tissue respiration, 300
PAAL, H. See Oehme, C., 276
PACHMURIN, K. See Raspopova, N. A., 736,
PACKARD, M., and H. F. WECHSLER. Chronic suprarenal insufficiency, 694
PAGE, E., See Lyons, W. R., 274
PAGET, M. See Langeron, L., 407, 722
Paget's disease and osteoporosis, 700
serum calcium, inorganic phosphorus and phosphatase activity in, 601
PAILLAS, J. See Olmer, D., 732
PAILLAS, J. E. See Cornil, L., 250
PAILLAS, J. E. See Olmer, J., 601
PAILLAS, J. E. See Roger, H., 701
PALACIOS, L. See Lipschütz, A., 593
PALLES, A. L. C. The influence of menformone upon ocular pressure, 713
PALMER, W. W., and J. P. LELAND. Comparative calorigenic action of normal and pathological thyroid glands administered in equi-thyroxine doses, 301
Pancreas, activity of islets of, 730
autonomic innervation of, 286
effect of anterior hypophysis extract on islet of, 284
effect of diet, lack of exercise and overeating on islets of, 131
effect of ingestion of, on blood lipids, 443
endocrine changes in, during gestation, 285
formation of cells of Langerhans in, 597
and galactose metabolism, 408

hyperglycemic substance from, 290
and hypophysis, 272
response of, to secretin, 132
Pancreatectomized-hypophysectomized dogs, dextrose tolerance curves of, in absence of insulin, 440
Pancreatectomy and adrenalectomy in the dog, 132
after hypophysectomy, 126
and carbohydrate metabolism of ducks, 733
effect of, on blood calcium, 286
effect of raw pancreas on blood lipids after, 443
non-essentiality of raw pancreas, lecithin or choline in survival after, 284
and parathyroids, 449, 600, 601
Pancreatic ducts, artesia of, accompanied by hyperinsulinism, 443
Pancreatrope factor of anterior lobe and blood sugar level, 262
Pancréotoxine for treatment of diabetes, 598
PAPADATO, L., and B. BAPKOWA. The intracranial endocrine glands and the hormones of the cerebrospinal fluid, 700
PAPANICOLAOU, G. N., and E. SHORR. The action of ovarian follicular hormone in the menopause, as indicated by vaginal smears, 712
Parabiosis, effect of, on estrus cycles, 276
effect of, on gonads in rats, 421
Parabiotic union, of female rats with castrated and hypophysectomized males, 275
Parathormone, action of, 601
Parathyroid adenoma, histology of, 451
and calcium therapy in chronic ulcerative colitis, 449
extract, action of, on carbohydrate metabolism, 600
extract and ardenal cortex lesions, 697
extract and bile composition, 699
extract, effect of, on the bones of hypophysectomized rat, 281
extract, effect of, on growth of axolotls, 451
extract and magnesium, 448
extract and urine electrolytes, 448
extract and viosterol, 450
glands and adrenalectomy, 695
glands, chronic insufficiency of, and follicular hormone, 450
glands, fluorine as specific for, 600
glands, hyperplasia of, and hyperparathyroidism, 133
glands, lipid contents of, 450
glands, normal structure of, 450
glands, origin of, in guinea pigs, 453
glands, and pancreatectomy, 449, 601
glands, physiology of, 134
glands, relation of, to insulin mechanism, 601
glands, relation of, to polyarthritis and spondyloarthritis, 601
hormone, action of, 448
hormone, action of, in hypophysectomized pigeons, 280
hormone, action of, on normal and tuberculous guinea-pigs, 449
hormone, mechanism of action of, 600
hormone, reaction of liquid ammonia on, 451
hormone, tests for, in blood, 448
hyperactivity and osteitis fibrosa cystica, 450
hyperfunction, treatment of, 134
influence on creatine and phosphoric acid metabolism, 134
tetany, neurologic mechanism of, 452
tetany reduced by bile-acids, 449
Parathyroidectomy, adrenin content of adrenals after, 239
and angiospatic syndromes, 133
and bile-acid production, 451
PARHON, C. I., S. M. MILCOU and M. SCHACHTER. A case of gynecomastia, 408
PARHON, C. I., and I. ORNSTEIN. Study of the lipid contents of the parathyroids in different species of animals, 450
PARHON, C. I., C. PARHON-STEFANESCU and I. ORNSTEIN. Rôle of cholesterol in thyro-ovarian antagonism. Ovarian and adrenal cholesterol in thyroidectomized and in thyrozin-fed animals, 736
PARHON, C. I., C. PARHON-STEFANESCU and E. TOMORUG. Studies on the influence of urine from acromegalics on the growth of young animals, 127
PARHON, C. I., and E. TOMORUG. Osteosis of parathyroid origin. Marked improvement following ovariectomy, 450
PARHON-STEFANESCU, C. See Parhon, C. I., 127, 736
PARIJSSKAYA, N. See Asimoff, G., 585
PARKER, G. H. What part of the melanophore system in Fundulus is acted upon by adrenalin? 573
PARKES, A. S. See Deanesly, R., 414, 704
PARKES, A. S. See Hill, R. T., 720
PARKINSON, J., and C. Hoyle. Thyrotoxic hypertension, 301
Parturition, hypophysis after, 283
PASQUALETTI, R. A. See Markee, J. E., 420
PASQUALINI, R. Q. Water metabolism in *Bufo arenarum* (Hens). Diuresis after total and partial hypophysectomy, 596
PASQUALINI, R. Q. Water metabolism in the toad. Diuresis in animals with experimental lesions of the infundibulotuberal region, 277
PASQUALINI, R. Q. Water metabolism in the toad. Water absorption in normal and hypophysectomized toads with ureters tied, 277
PASSEK, V., and M. RUBINSTEIN. Antitrypsin of blood serum as affected by transplantation of endocrine glands, 408
PASSEK, V., and M. RUBINSTEIN. Glycemia and transplantation of the endocrine glands, 700
PAUL, W. D. See Clark, B. B., 284
PAWLIKOWSKI, T. Incretory vacuoles in the adrenalinogenuous cells of the medulla of guinea pig adrenals, 573
PAYNE, W. W. See Ellis, R. W. B., 443
PEARL, R., M. GOOCH, J. R. MINER and W. FREEMAN. Endocrine organ weights and somatological habitus types, 700
PEARSON, O. H. See Salter, W. T., 460
PEARSON, P. B. See Catchpole, H. R., 265
PECZENICK, O. See Kun, H., 418
PEDERSEN-BJERGAARD, K. Titration of estrin and gonadotropic hormone in urine, 422
PEDERSEN-BJERGAARD, K. See Thomsen, O., 726
Pelvic structure, effect of folliculin on, in male mice, 416
PENCHARZ, R. I. see Anselmino, K. J., 409
PENCHER, H. F. Creatine metabolism in infancy and childhood; case of Thomsen's disease cured by thyroid extract, 301
PENNINGTON, W. D. See Jensen, H., 730
PERAUS, A. Changes in the arrangement of fat in the cells of the corpus luteum of pseudogestation in rabbits, 422
PERAUS, A. See Skowron, S., 424
PERIA, D. Effect of suprarenal cortical hormone on the natural resistance of pituitarectomized rates, 245
Periodic fertility, guide to, 255
PERKIN, H. J., F. H. Lahey and R. B. Cattell. Blood iodine studies in relation to thyroid disease, 459
PERLA, D. Effect of anterior hypophysis emulsion on natural resistance of hypophysectomized and normal rats to histamine poisoning, 438
Personality and endocrines, 406
PETER, F. Analysis of the influence of the anterior hypophysis hormone on oxygen consumption, 277
PETERS, J. P. See Man, E. B., 288
PETERSON, Social aspects of diabetes; a study of sixty cases, 289
PETTIS, J. H., and E. D. SORSKY. Thyroid gland ablation. Its use for congestive heart failure and angina pectoris, with a report of five cases, 736
PEYSAKHOVICH, I. M. Lutoestrogen, gonadotropic hormone from onions, 422
PFEIFFER, C. A. Sexual differences of the hypophyses and their determination by the gonads, 439
PFEIFFER, C. A. See Du Shane, G. P., 432
PFEIFFER, C. A. See Witschi, E., 442
PFIFFNER, J. J., W. W. SWINGLE and H. M. VARS. Cortical hormone requirement of adrenalectomized dog, with special reference to method of assay, 245
PFIFFNER, J. J., and H. M. VARS. Extraction studies on the adrenal cortical homone. Distribution studies, 245
PFIFFNER, J. J., H. M. VARS and A. R. TAYLOR. Extraction studies on the adrenal cortical hormone. Methods of preparation, 116
PFIFFNER, J. J., O. WINTERSTEINER and H. M. VARS. Chemical studies on the adrenal cortex. Fractionation studies on hormone concentrates, 245
PFIFFNER, J. J. See Vars, H. M., 247
PFIFFNER, J. J. See Wintersteiner, O., 248
PHLLIPS, F. J. See Curtis, G. M., 734
PHILLIPS, P. H., H. ENGLISH and E. B. HART. The augmentation of the toxicity of fluorosis in the chick by feeding desiccated thyroid, 460
PHILLIPS, R. B. Theelin therapy in vulvovaginitis, 259

Phosphate activity of bone and kidney, influence of growth hormone on, 283
Phosphoric acid, influence of parathyroid on metabolism of, 134
PICARD, D. One method of formation of the cells of Langerhans in the pancreas, 597
PICARD, D. See Florentin, P., 285, 730
PICHA, V. See Stimmel, B. F., 725
PICK, E. P. See Glaubach, S., 605
PIGHINI, G. An experimental contribution to the study of the interrelations between the hypophysis, the thyroid glands and the testes, 117
PIGHINI, G. Modifications of the thyroid gland under various experimental conditions (deficiency or excess of iodine, of anterior pituitary hormone, of calcium), 301
PIGHINI, G. The new investigations on the etiology of endemic goiter, 302
PIGHINI, G., and C. F. PORTA. The reintegrative action of the anterior pituitary of the ovarian extracts upon the experimental changes of the nasal mucous membranes and nasal bones produced by castration, 121
Pigmentation, action of thyroid hormone on, in birds, 306
PILCHER, C. See Wilkins, W. E., 283
Pilocarpine, effect of, on submaxillary gland, 404
PINCUS, G., and R. E. KIRSCH. The sterility in rabbits produced by injections of oestrone and related compounds, 713
PINCUS, G. See Burdick, H. O., 119
Pineal body, hormone properties of, 574
and cerebro-spinal fluid, 700
extract, effect of, on growth and development, 408, 701
gonadotropic action of, 452
synergistic action with pregnancy urine, 452
weights in rats, normal and castrate, 586
PIRCHAN, A., and E. KODIČEK. The metabolism of sulphur and its elminiation through the urine after charging the organism with thiosulphate, 701
PISA, M. See Coppo, M., 448
Pitocin effect of, on protein, water and mineral metabolism, 728
Pitressin and blood vessels, 703
diuresis and blood pressure effects of, 128
effect of, on protein, water and mineral metabolism, 728
test, clinical experiments with, 725
Pituitrin, effect of, on protein, water and mineral metabolism, 728
sensitivity of excised uterus, 259
Placenta, corpus luteum hormone in, 251
extract and erythrophore expansion, 409
extract, inhibiting action of, 425
physiology of maternal, 423
and pregnancy hormone, 273
rôle of, in maintenance of pregnancy, 706
Plant growth, and anterior pituitary extract, 277, 595
Plants, action of thyroxin and folliculin on, 295
Plasma minerals, effect of anterior pituitary extract on, 587
PLAUT, F., and M. BULOW. Decrease of vitamin C in cerebrospinal fluid as a criterion of increased metabolic rate in malaria and experimental hyperthyroidism, 302
Plumage, effects of thyroxin on, 458
Pluriglandular insufficiency, 117
PODLESCHLA, K. Investigations of the pituitrin sensitivity of the exercised human uterine muscle under physiologic conditions, 259
PODROUZEK, V. See Bergauer, V., 291
POHLE, W. D. See Hartman, F. A., 690
Polyuria and diabetes insipidus, 279
POMERAT, C. M. Experimental studies on the nuptial pads of male Triturus viridescens, 713
POPA, G. T., and U. FIELDING. Expansion of the melanophores under the influence of extracts of anterior hypophyseal lobe mixed with red blood cells, 278
PORKHOVIK, J. See Wittenbourg, W., 715
PORTA, C. F. See Pighini, G., 121
PORUMBARA, I. See Zaharesco-Karaman, 426
Postlobin-V and hyperglycemia, 432
Potassium iodide, cytological response to treatment with, 296
POWELL, T. O. See Hinman, F., 707
Precocious development of ovaries induced by artificial light, 578
Precocity, sexual, due to adrenal cortical tumor, 244
Pregnancy, odrenal cortical therapy in vomiting of, 240, 247
biochemical test for, 278
blood lipid changes in, 410
blood, parathyroid hormone from, 449
comparison of tests for, 590
and diabetes, 130, 730
diagnosis of, 254, 412, 419, 423, 426
and diuresis, 273
effect of corpus luteum, removal on, 578
effect of folliculin injections on, 579
fish test in diagnosis of, 257
and Graves' disease, 453
histidine test for, 711
hormone investigations in vomiting of, 427
hormone and placenta, 273
in hyperthyroidism, 735
hypophysis during, 283, 589
maintenance of, after ovariectomy, 706
progestin in functional disorders of, 703
prolongation, of, 706
rapid tests for, 411
and survival period after adrenalectomy, 571
test, 705, 714
urine, assay of estrin in, 709
urine and blood cholesterol, 273
urine effect of, on dogs and apes, 709
urine, effect of luteinizing factor of, on gonads of immature rats, 591
urine extract, effect of on hypophysis, 272
urine extract, effect of on ovary, 121, 706
urine extract, effect of prolonged injection of, on anterior hypophysis, 442
urine extract, effect of, on uterus, 718
urine, extraction of chystalline by-product of, 415
urine extracts in excessive uterine bleeding, 715
urine, gonadotropic hormone of, 708
urine gonadotropic hormone, assay of, 434
urine injections and hypophysis, 267
urine, non-effect of estrin in augmentation of action of, 433
urine, preparation of gonadotropic extract of, 272
urine, titration of, 267
vitamin C in corpus luteum during, 410
Pregnant mare serum, effect of, on follicular development, 724
effect of injection of, in chickens, 275
Pregnyl, effect of, on pregnant rats, 585
PRENDERGRASS, E. P. See Rose, E., 737
Pressor factor in cerebrospinal fluid, 586
and oxytocic hormones, their purification and chemistry, 282
PRIBRAM, H. Clinical observation on the percutaneous effects of insulin in diabetic patients, 446
PRICE, J. B. See Danforth, C. H., 406
PROBSTER, A. Hormone studies on corpus luteum cyts, 260
Progesterone, effect on uterus, testicles and hypophysis, 252
relation of vitamin C to, 410
Progestin content of corpora lutea of cows, 709
formation of, by placenta, 706
indications for clinical use of, 703
inhibition of follicular hormone by, 416
isolation of chystalline, 248
use of, in threatened and habitual abortion, 256
and uterine contractions, 581
Proclactin, assay of, in different types of cattle, 122
effect of, on estrus cycle, 580
maternal behavior induced by, 280
in pituitaries of maternalized (thyroidectomized) male rats, 437
preparation of, 263
relation of, to pregnancy cells and eosinophiles in hypophysis, 435
response of adult rat testes and adrenals to, 280
Prolan, disappearance of, 274, 594
effect of, on agglutinin response to B. pertussis, 267
effects of divided dosage in male rat, 429
fats of, 274
influence of, on egg-production, 426
in treatment of Simmonds' disease, 270
A in teratoma testis, 250
B in corpus luteum cyst, 260
Prostrate, changes in after folliculin, 256
effect of sex hormone on, 427
influence of folliculin on, in young apes, 414
weight, in assay of gonadotropic hormone, 434
Prostatic hypertrophy, endocrine relationships of, 251, 415
endocrine therapy of, 711
Protamine insulinate, clinical experience with, 446
Protein, endogenous carbohydrate formation from, 403
metabolism, effect of adrenalin on, in work, 114
metabolism and hypophysis, 721
specific dynamic action of, in hypothyroidism,

298
PROUST, R., R. MORICARD and P. RODIER. The increased rate of elimination of the anterior pituitary hormone in the urine in cases of metropathies of ovarian origin, 278
Pruritis, treatment of with estrogens, 880
Pseudopregnancy in rabbits, corpus luteum in, 422
Psychic disturbance of menstrual cycle, endocrine therapy of, 575
Psychophysical treatment and diabetes, 442
Psychoses, comparative investigation of the testes in, 583
and psychoneuroses in hyperthyroidism, 735
and thyroid disorders, 297
PTCHELINA, V. See Asimoff, G., 585
Pubertas praecox from adrenal tumor, 572
with tumour in floor of third ventricle, 576
Puberty, law of and ovarian damage, 256
PUGSLEY, L. I. The effect of thyrotropic hormone upon serum cholesterol, 278
PUGSLEY, L. I., and E. ANDERSON. The effect of administration of calciferol on the increased calcium excretion induced ty thyroxine, 302
PUGSLEY, L. I., and E. ANDERSON. The effect of desiccated thyroid, irradiated ergosterol and ammonium chloride on the excretion of calcium in rats, 736
PUGSLEY, L. I. See Collip, J. B., 600
PUTMAN, T. J. See Salter, W. T., 280
Pyogenic infections, adrenal cortical extract in, 247

QUIRLL, O. Absence of the hypophysis in a case of chondrodystrophie, 439

RABINOWITCH, I. M., and A. F. FOWLER. Respiratory metabolism studies in hyperinsulinism following ingestion of glucose, 289
RADEFF, I. N. The results of glandular therapy in mongolian idiots, 408
Radiation in thyroid diseases, 609
Radium destruction of hypophysis, 436
effect of, on hypophysis, 273
and ovarian function, 714
RAND, C. W., and R. G. TAYLOR. Irradiation in treatment of tumors of pituitary gland; report of twenty-three cases, 722
RANDALL, L. O. See Jordan, W. R., 599
RANDALL, S. S. See Gulland, J. M., 718
RANSOM, S. W. Somnolence resulting from lesions in the gypothalamus, 278
RANSOM, S. W. See Fisher, C., 433, 587.
RAPPAI, S., and P. ROSENFELD. Metabolism of animals injected with thyroxin and vitamin A, 460
RASPOPOVA, N. A., K. PACHMURIN, C. VOLKOVISSKAJA, P. VOLOBUIEFF, W. BOGDANOVA, N. ARSAMASZEVA and W. IVANOVA. Influence of hyperthyroidization on repeated moulting in geese, 737
Rathke's Pouch, tumor of, and Simmonds' disease, 590
RATSIMAMANGA, R. See Giroud, A., 269
RAVDIN, I. S. See Elsom, K. A., 448
RAY, S. N. See Harris, L. J., 241
RAYNAUD, R. See Courrier, R., 250
Raymaud's disease and sympathectomy, 115
READ, L. S. See Chaikoff, I. L., 123
READING, B. Theelin in the treatment of gonococcus vaginitis in children, 260
REGEN, E. M. See Wilkins, W. E., 283
Regeneration in axolotls and hypophyseal extract, 264
REGIDOR, P. P. See Haro, F., 706
REICHERT, F. L. See Chaikoff, I. L., 123, 431
REICHSTEIN, T. Cortical hormone, 694
REICHSTEIN, T. On the constituents of the adrenal cortex, 875
Reid-Hunt reaction and thyrotropic hormone, 100, 276
REISS, M. Die Hormonforschung und ihre Methoden, 236
REISS, M., L. SCHWARTZ and F. FLEISCHMAN. Dehydration processes in tissues of thyroxin-treated animals, 302
REISS, M., L. SCHWARTZ and F. FLEISCHMAN. Relation between anterior pituitary growth hormone and protein metabolism, 723
Relaxation and diabetes, 442
REMZI, T. Site of formation of gonadotropic substances, 439
Renal failure, acute, in diabetic coma, 287
insufficiency and hyperparathyroidism, 448
RENNIE, J. L. Diabetes mellitus following mumps, 290
Reproduction in chimpanzee, 122
effect of litter size on growth, 418
influence of Vitamins B and G on, 698
physiology of, 258, 417
cycle, metabolism of women during, 583
organs of the ewe, control of, 413
Resistance to toxin, influence of adrenal cortex on, 570
RESNIK, H. Jr., and B. FRIEDMAN. Studies on the mechanism of the increased oxygen consumption in patients with cardiac disease, 302
Respiration of tissues, action of secretin on, 288
Respiratory metabolism, effect of glucose on, after adrenalectomy, 572
metabolism, studies in, 289
quotient, action of adrenalin on, 403
REY, P. Action of extracts of the posterior hypophysis on the water exchange in frogs, 279
REYNOLDS, S. R. M. Some structural and functional features of rabbits' uteri following prolonged oestrin administration, 713
RHEA, L. F. See Howard, C. P., 590
RHODEN, E. See Hoffman, F., 449
RICHARD, G. Technique for studying endocrine activity of serum, 701
RICHARDSON, H. B. See Shorr, E., 305
RICHMOND, G. M. See Luck, J. M., 244
RICHTER, C. P. Experimental diabetes insipidus; its relation to the anterior and posterior lobes of the hypophysis, 128
RICHTER, C. P. The primacy of polyuria in diabetes insipidus, 279
RICHTER, C. P., and J. F. ECKERT. Further evidence for the primacy of polyuria in diabetes insipidus, 279
Rickets, the epiphyses in, 305
RIDDLE, O., R. W. BATES and E. L. LAHR. Prolactin induces broodiness in fowl, 596
RIDDLE, O., and L. B. DOTTI. Action of parathyroid hormone in normal and hypophysectomized pigeons, 280
RIDDLE, O., E. L. LAHR and R. W. BATES. Maternal behavior induced in virgin rats by prolactin, 280
RIDDLE, O., E. L. LAHR, C. S. MORAN and R. W. BATES. Response of adult rat testes sex accessories and adrenals to injections of prolactin, 280
RIDDLE, O., and J. P. SCHOOLEY. Absence of follicle-stimulating hormone in pituitaries of young pigeons, 279
RIDDLE, O., and G. C. SMITH. The effect of temperature on the calorigenic action of dinitrophenol in normal and thyroidectomized pigeons, 303
RIDDLE, O., G. C. SMITH and C. S. MORAN. Effects of complete and incomplete hypophysectomy on basal metabolism of pigeons, 279
RIDDLE, O. See Bates, R. W., 122, 263, 428
RIECKHOFF, W. See BRÜHL, R., 411
RIETTI, C. T. Ketonuria produced by anterior pituitary alkaline extract, 596
RIETTI, C. T. See Houssay, B. A., 125
RIML, O. See Engelhart, E., 581
RING, G. C. Calorigenic action of fat and carbohydrate in pancreatic diabetes, 290
RING, G. C. The specific dynamic action of protein in pancreatic diabetes, 732
RISEMAN, J. E. F., D. GILLIGAN and H. L. BLUMGART. Treatment of congestive heart failure and angina pectoris by total ablation of the normal thyroid gland. The sensitivity of man to epinephrine injected intravenously before and after total thyroidectomy, 737
RISEMAN, J. E. F. See Ernstene, A. C., 597
ROBB, P. D. See Scharles, F. W., 409
ROBERTS, R. G., W. R. TWEEDY and G. H. SMULLEN. Some reactions of ammonolyzed parathyroid hormone, 451
ROBERTSON, J. D., and A. T. WILSON. Basal metabolism and impedance angle in thyrotoxicosis, 303
ROBINSON, C. S. See Kraft, R. M., 120
ROBINSON, S. K. Hyperthyroidism masked as essential hypertension, 460
ROBSON, J. M. The action of the ovarian hormones on the uterus muscle measured in vivo and in vitro, 581
RODEWALD, W. See Koller, G., 272
RODIER, P. See Proust, R., 278
ROGOFF, J. M. Addison's disease following adrenal denervation in case of diabetes mellitus, 694
ROGOFF, J. M. See Schour, I., 695
ROJAS, P., and E. DE ROBERTIS. Golgi apparatus in follicular cells of the ovary of Jenynsia lineata, 260
ROOST, G. See Bastenie, P., 602

ROOT, H. P., P. WHITE, A. MARBLE and E. H. STOTZ. Clinical experience with protamine insulinate, 446
ROOT, H. F. See Joslin, E. P., 599
ROOT, H. F. See Marble, A., 289
ROOT, S., F. MERRILL and A. TIMPARELLI. Salt therapy in Addison's disease, 246
ROSE, E., E. K. ROSE and E. P. PRENDERGRASS. The treatment of hyperthyroidism in children and younger adolescents, 737
ROSE, E. K. See Rose, E., 737
ROSENBLUETH, A. See Cannon, W. B., 113
ROSENBLUETH, A. See Liu, A. C., 244
ROSENFELD, P. See Rappai, S., 460
ROSENKRANZ, K. D. The thyroid at the menopause, 460
ROSS, J. M. See Hare, D. C., 692
ROSS, R. A. See Hamblen, E. C., 706
ROSTAND, J. The effect of urine from a baby on tadpoles, 701
ROSTAND, J. The stimulation of ovulation in different frogs and toads, 439
ROTH, P. Effects of human pathological thyroid on batrachian metamorphosis, 303
ROTHMANN, H. Diagnosis and treatment of hypophyseal emaciation, 439
ROTHCHIELD, F., H. STAUB and K. MEZEY. Effect of thyreotropic hormone preparation of anterior lobe on diuresis in the white mouse and on blood pressure of the cat, 128
ROUSSEL, G. See Gallot, G., 582
ROUSSY, G., and M. MOSINGER. On the intermediate lobe of the hypophysis. The hypophyseal cleft and adjacent structures, the immigration of glandular cells into the nervous lobe, 280
ROUSSY, G., and M. MOSINGER. The neurocrine pigmentation of the hypophysis and peripheral neurocrine action, 440
ROGER, H., J. ALLIEZ and J. E. PAILLAS. Progressive lipodystrophy, 701
ROWE, A. W. The metabolism of galactose. The influence of disturbed endocrine. The influence of tolerance of coexisting endocrinopathies, 408
ROWNTREE, L. G., J. H. CLARK, A. STEINBERG, N. H. EINHORN and A. M. HANSON. Further studies on the thymus and pineal glands, 701
ROWNTREE, L. G., J. H. CLARK, A. STEINBERG, A. M. HANSON, N. H. EINHORN and W. A. SHANNON. Further studies on the thymus and pineal glands, 408
RUBENSTEIN, M. See Passek, V., 700
RUBIN, M. I., and E. T. KRICK. Effect of adrenalectomy on salt metabolism in rats, 115
RUDY, A., and B. SACHS. Transitory visual disturbances in diabetes mellitus, 446
RUEDIGER, E. H. The Aschheim-Zondek test for pregnancy, 714
RUSSEL, W. Exophthalmos following the administration of thyroid extract, 738
RUSSELL, D. S. See Aitken, R. S., 262
RUSSELL, D. S. See Crooke, A. C., 691
RUSSELL, D. S. See Le Marquand, H. S., 576
RUTISHAUSER, E., and P. GUYE. Grafts of adrenals from newborn animals into rats, 695

SABRAZÈS, J., F. LE CHUITON and G. GINESTE. Hyperplasia of the glands of the skin and sudoriferous tumors in albino rats injected with folliculin, 260
SACHS, B. See Rudy, A., 446
SAETHRE, H. Excretion of prolan in advanced age and in the very aged, 723
SAINTON, P., F. KAYSER and E. ANSCHEL. Study on the elimination of iodine following ingestion of diiodotyrosine, 303
SAKHAROFF, G. P., and D. M. ROSSIYSKY. New method of treatment for diabetes, 598
SALLET, J. See Baudouin, A., 239, 402
SALMON, U. J. See Frank, R. T., 268, 434
Salt treatment in Addison's disease, 115, 246
SALTER, W. T., A. GREEN and T. J. PUTNAM. A method for quantitating the reducing substance of the anterior hypophysis, 280
SALTER, W. T., and J. LERMAN. The genesis of thyroid protein: clinical assays of artificial thyroid protein in human myxedema, 690
SALTER, W. T., and J. LERMAN. The metabolic effects of human thyroglobulin and its proteolytic cleavage products, 303
SALTER, W. T., and O. H. PEARSON. The enzymatic synthesis from thyroid diiodotyrosine peptone of an artificial protein which relieves myxedema, 460
SALTER, W. T. See Eppinger, E. C., 455
SALTER, W. T. See Scharles, F. W., 409
SAMAAN, A. The effect of pituitary (posterior lobe) extract upon the urinary flow in non-anaesthetized dogs, 130
SAMISCH, Z. See Morgan, A. F., 450
SAMMARTINO, R. See Houssay, B. A., 242, 449, 589, 601, 721
SAMPSON, M. M. See Coplan, H. M., 454
SANDBERG, M., and D. PERLA. Nitrogen and sulfur metabolism in suprarenalectomized rats, 695
SANDERS, J. M. The development of the thyroid gland in urodeles, 738
SANKARAN, S. See McCarrison, R., 609, 699
SANTA, N. See Gradinesco, A., 571
SAPKOWA, B. See Papadato, L., 700
Sarcoma in male mice and estrogenic hormones, 705
SARDI, J. L. Lactation in male guinea pigs treated with anterior hypophyseal extract, 723
SARDI, J. L. Lactogenic effect of anterior pituitary extract in the male guinea pig, 723
SARIC, R. See Aubertin, E., 729
SAUNDERS, F. J., and H. H. COLE. Age and the qualitative response of the immature rat to the mare gonadotropic hormone, 724
SAUNDERS, F. J., and H. H. COLE. Means of augmenting the ovarian response to gonadotropic substances, 724
SAUNDERS, F. J., and H. H. COLE. Two gonadotropic substances in mare serum, 723
SAVINO, E. Immunization of hypophysectomized dogs with diptheria antitoxin, 280
SAWIZKI, W. The relations between the breast and the internal secretions, 260
SCHACHTER, M. See Parhon, C. I., 408
SCHAEFFER, G. See Le Breton, E., 298
SCHARLES, F. H., P. D. ROBB and W. T. SALTER. Liver amylase: The effect of nutrition and of hormones, 409
SCHEFFER, L., and L. MEGAY. Iodine metabolism in goiter, 303
SCHEFFER, L. See Mansfeld, G., 608
SCHENK, F., and H. LANGECKER. Changes in the adrenal cortex of the rabbit after prolonged administration of insulin, 695
SCHNEIDER, P. F. A syndrome suggestive of estrogenic deficiency, 714
SCHEPS, M. Histological aspect of lesions of the liver and kidneys after injections of vasopressin in animals, 281
SCHEPS, M. Influence of vasopressin on the cardiovascular system of animals, 280
SCHEPS, M. See Elmer, A. W., 240, 293, 604
SCHILLER, M. B. Action of monobromacetic acid on sexual function in the rat, 260
SCHILLER, M. B. The adrenals and sexual function in the rat, 246
SCHMIDT, E. G., J. S. EASTLAND and J. H. BURNS. A comparative study of glucose and sucrose tolerance tests, 447
SCHMIDT, I. G. The excretion of theelin in the urine of guinea pigs with irradiated ovaries, 423
SCHMULOVITZ, M. J., and H. B. WYLIE. The chemical diagnosis of pregnancy by detection of estrin in urine, 423
SCHNEIDER, E., and E. WIDMANN. The hepatohormonal direction of vitamin A metabolism and the etiology of Paget's disease, 451
SCHOCKAERT, J. A. The gonadotropic hormone content of human anterior hypophyses, 128
SCHOCKAERT, J. A. The sex hormones of the female, 121
SCHOCKAERT, J. A., and J. LAMBILLON. Note on the presence of a substance antagonistic to vasopressin in the blood of pregnant women, 724
SCHOCKAERT, J. A., and A. LEJEUNE. The vasopressin content of hypophyses from normal guinea pigs and those injected with folliculin and thyroxin, 724
SCHOEDEL, W. Estimation of the thyreotropic activity of the anterior pituitary gland upon the basal metabolism, 128
SCHONIG, W., and Sturm, A., 305
SCHÖNBRUNNER, E. See Lasch, F., 731
SCHOOLEY, J. P. See Riddle, O., 279
SCHOUR, I., and J. M. ROGOFF. Changes in the rat incisor following bilateral adrenalectomy, 695
SCHRAIBER, J. See Goldemberg, L., 455, 605
SCHROEDER, H., and F. DORMANN. Thyroxin action and vitamin C in the tadpole, 738
SCHULTZ, A. H., and F. F. SNYDER. Observations on reproduction in the chimpanzee, 122
SCHULTZER, P. Importance of the operative technique

on the results of bilateral adrenalectomy in young rats, 246
SCHULTZER, P. Influence of extracts of adrenal cortex on young rats deprived of their adrenals and the survival time of these animals after cessation of hormonal treatment, 246
SCHUMACHER, P. Action of anti-thyroid protecting substance on lactation, 702
SCHWABE, E. L. See Emery, F. E., 119
SCHWARTZ, H. G., and C. L. BUXTON. The effect of sympathetic denervation upon ovulation and estrus in the rat, 423
SCHWARTZ, L. See Reiss, M., 302, 723
SCHWARTZBACH, S., and E. UHLENHUTH. Physiology of the thyreoactivator in amphibia. Increased oxygen consumption following injection of thyreoactivator, 724
SCHWARTZBACH, S. S. See Uhlenhuth, E., 739
SCHWARZ, C. See Hamilton, B., 733
Sclerosis, pluriglandular, clinical aspects and morbid anatomy in, 117
SCOTT, A. H. Thyroxin and tissue metabolism, 304
SCOTT, D. A., and A. M. FISHER. The effect of zinc salts on the action of insulin, 290
SCOWEN, E. F., and A. W. SPENCE. Effect of prolonged administration of acid extract of anterior pituitary on the thyroid gland of guinea-pigs, 440
SCOWEN, E. F. The use of gonadotropic hormone in the treatment of imperfectly migrated testes, 423
SCOZ, G. The action of thyroxine and anterior pituitary extract on hair growth, 738
Scrotal function and male sex hormone, 258
SECHER, K., and J. VESTERDAL-JÖRGENSEN. Experimental investigation of the size of the heart during and after feeding with thyreoidin, 304
Secretin, effect of, on Brunner's glands, 444
Sedimentation rate and diabetes, 445
SEELKOPF, K. See Grabe, F., 575
SEEVER, M. H., and H. A. BRAUN. Effect of sodium fluoride upon experimental thyroid poisoning, 738
SEREJSKI, M., and R. TOPSTEIN. Endocrine insufficiency and the brain, 304
SELLE, R. M. The embryology of the thyroid, parathyroid and thymus of the Pacific pallid bat, 117
SELYE, H. The alarm reaction, 876
SELYE, H., J. B. COLLIP and D. D. THOMSON. The effect of gonadotropic hormones during gestation and lactation, 281
SELYE, H., and T. MCKEOWN. Studies on the physiology of the maternal placenta in the rat, 423
SELYE, H., and T. MCKEOWN. Further studies on the influence of suckling, 261
SELYE, H., H. MORTIMER, D. L. THOMSON and J. B. COLLIP. Effect of parathyroid extract on the bones of the hypophysectomized rat, 281
SELYE, H., D. L. THOMSON and J. B. COLLIP. Metaplasia of uterine epithelium produced by chronic oestrin administration, 261
SELYE, H. See Bachman, C., 263
SELYE, H. See Collip, J. B., 600
SELYE, H. See McEuen, C. S., 711
Seminal tract, ligation of, and testis, 256
vesicle, effect of estrin and male hormone on, 421
vesicle growth as test for pregnancy, 426
vesicles of prolan-treated infantile rate, 591
vesicles, substances affecting, 879
SEWARD, B. P. A clinical study of the mild grades of hypothyroidism, 304
Sex cycle modification and exposure to light, 410
cycle and thyroid, 434
difference in gonad-stimulating potency of hypophysis in gonadectomized rats, 424
hormone, effect of, on metabolism of sex organs, 577
hormone, influence of, on adrenal cortex, 252
hormones, effect of, on plumage and eye-color of blackbird, 704
hormones, effect of, on prostate of monkeys, 427
hormones, procedure for quantitative extraction from urine, 416
inversion and sex ratios, 705
offenders, results of castration in, 254
of fetus, diagnosis of, 274
ratios and sex inversion, 705
reversal and male hormone, 579
reversal produced by folliculin, 579
reversal in transplanted gonads in amphibia, 708
specificity of creatin metabolism, 418
SEXTON, D. L. The endocrines in gastrointestinal disorders, 702
Sexual development, premature, cause of, 417
function and water economy, 428
function, influence of monobromacetic acid on, 260
hormone, site of formation of, in the normal gravid female, 582
periodicity in relation to cytological changes in pituitary, 442
predisposition to disease, 418
SGROSSO, J. A. Denervation of the adrenals and adrenalin secretion, 246
SGROSSO, J. A. Effects of adrenal enervation on adrenalin secretion, 695
SHANNON, W. A. See Rowntree, L. G., 408
SHARPE, J. C., and J. D. BISGARD. The relation of the thyroid gland to hematopoiesis. Experimental total thyroidectomy in the rabbit, 739
SHELLING, D. H. The parathyroid glands in health and in disease, 236
SHEPARDSON, H. C. See Escamilla, R. F., 293
SHIBATA, R. Studies on the detoxicating hormone of the liver, 702
SHKUROV, B. I., and K. F. ELENEVSKIY. Histologic study of parathyroids in chronic rheumatic polyarthritis and spondyloarthritis, 601
Shock and adrenal cortical extract, 241
adrenin production in, 239
SHOCK, E. D. See Jensen, H., 730
SHORR, E., H. B. RICHARDSON and H. G. WOLFF. Endogenous glycine formation in myopathies and Graves' disease, 305
SHORR, E. See Papanicolaou, G. N., 712
SHRADER, L. C. See Griffiths, E. P., 286
SICNASI, B. See Olmer, J., 601
SIEBKE, H. See Schockaert, J. A., 128
SIGNORELLI, J., H. HOSEN and J. M. MILES. The epiphyses in rickets, syphilis and thyroid deficiency, 305
SILBERBERG, M. Effects of extract of cattle anterior pituitary gland on endochondral ossification in young guinea pigs, 281
SILBERBERG, M., and R. SILBERBERG. Influence of acid extract of cattle anterior pituitary gland on bone repair in young guinea pigs, 440
SILBERBERG, R. See Silberberg, M., 440
SILVETTE, H., and S. W. BRITTON. Carbohydrate and electrolyte changes in the opossum and marmot following adrenalectomy, 876
SIMON, E. The effect of the antithyreotrope factor of the blood on thyroid gland activity, 725
SIMON, H. E. Myasthenia gravis: effect of treatment with anterior pituitary extract, 724
Simmonds' disease, 262, 264
in adolescent girl, 602
and atrophy of anterior hypophyseal lobe, 269
due to tumor of Rathke's Pouch, 590
and prolan therapy, 270
SIMON, A., and Z. KARDOS. The amount of blood-pressure and uterine-active substances in the posterior pituitary lobe of normal and thirsting animals, 281
SIMPSON, M. E. See Evans, H. M., 268
SIMPSON, S. L., M. DENNISON and V. KORENCHEVSKY. Some effects of adrenalectomy in male rats, 246
SIMPSON, S. L. See Korenchevsky, V., 418, 434, 711
SINDONI, A., JR. Optimum time to administer insulin, 732
SIPPE, C. A case of undescended testes successfully treated with antuitrin S., 714
SIWE, S. Retention of vitamin C in Addison's disease, 115
SIWE, S. Sodium chloride therapy in Addison's disease, 115
Skin decoloration in hypophysectomized toads, 263
SKOWRON, S., and A. PERAUS. Does folliculin terminate pregnancy by interfering with the function of the corpus luteum? 424
Skull of sheep, effect of thyroid deficiency on, 306
SMITH, C. Daily erythrocyte counts in menstrual and intermenstrual periods, 702
SMITH, D. C., and A. G. MULDER. The effect of accelerator nerve stimulation and of adrenalin on recovery from ventricular fibrillation in the cat, 876
SMITH, E. L. See Goldberg, L. E., 119
SMITH, E. R. See Dodds, E. C., 125
SMITH, F. M. See Cahill, G. F., 570
SMITH, G. C. See Riddle, O., 279, 303
SMITH, G. M. See Gardner, W. U., 416, 705
SMITH, G. VAN S. Recrudescence of ovarian function after heavy irradiation, 714
SMITH, G. VAN S., and O. W. SMITH. Comparatively low levels of oestrin in cases of chorio-epithelioma and hydatidiform mole, 122
SMITH, H. L. See Magee, H. R., 457

SMITH, J. See Grave, B. H., 705
SMITH, M. G. See Loeb, L., 419
SMITH, O. W. See Smith, G. van S., 122
SMITH, P. E. See Engle, E. T., 415
SMITHWICK, R. H., J. C. FREEMAN and J. C. WHITE. Effect of epinephrine on the sympathectomized human extremity; an additional cause of failure of operations for Raynaud's disease, 115
SMULLEN, G. H. See Roberts, R. G., 451
SNELL, A. M. The present status of the diagnosis and treatment of Addison's disease, 116
SNELL, A. M. The treatment of Addison's disease, 696
SNELLING, C. E., and I. H. ERB. Suprarenal atrophy, 696
SNYDER, F. F. See Schultz, A. H., 122
SNYDER, J. C. See Whitelaw, G. P., 247
Sodium and adrenal insufficiency, 244
chloride deficiency and Addison's disease, 694
chloride, effect of, on carbohydrate metabolism and blood pressure in diabetes, 731
chloride therapy in Addison's disease, 115
dinitrophenol and metabolic stimulants, 573
SOFFER, L. J. See Harrop, G. A., 114, 241
SOLOWAY, D. See McCahey, J. F., 421
SORSKY, E. D. See Pettis, J. H., 736
SOSKIN, S., I. A. MIRSKY, L. M. ZIMMERMAN and R. C. HELLER. Normal dextrose tolerance curves, in the absence of insulin, in hypophysectomized-depancreatized dogs, 440
SOSKIN, S. See Freed, S. C., 415
SPAYING, effect of, on tissue metabolism, 715
SPENCE, A. W. See Scowen, E. F., 440
Spermatic artery, effects of ligation of, 275
Spleen and sulfur metabolism, 407
Splenectomy, effect of insulin on sulfur metabolism after, 407
SLOTTA, K. H. See Allen, W. M., 576
Specific dynamic action of proteins in diabetes, 732
SPRAGUE, H. B. See Clark, R. J., 454
SPRAGUE, R. G., B. B. BLUM, A. E. OSTERBERG, E. J. KEPLER and R. M. WILDER. Clinical observations with insulin protamine compound, 733
SPRAGUE, R., and A. C. IVY. Studies in avian carbohydrate metabolism, 733
STACEY, R. S. See Goadby, H. K., 448, 601
STAHL, J., D. W. ATCHLEY and R. F. LOEB. Observations on adrenal insufficiency, 405
STAHL, J. See Loeb, R. F., 244
Staining methods for hypophysis, 431
STANCA, C. Local hormone therapy of ovarian insufficiency, 261
STANOJEVIĆ, L. See Mislowitzer, E., 276
STAUB, H. See Rothschild, F., 128
STEFKO, W. H. Constitutional anatomical peculiarities of organs from the standpoint of postnatal development, 118
STEGGERDA, F. R., and H. E. ESSEX. Comparative study of effects of preparation of posterior lobe of pituitary gland on water interchange in frogs, 282
STEHLE, R. L., and A. M. FRASER. The purification of the pressor and oxytocic hormone of the pituitary glands and some observations on the chemistry of the products, 282
STEHLE, R. L. A method for obtaining a preparation of the melanophore hormone of the pituitary gland, 725
STEHLE, R. L., K. I. MELVILLE and F. K. OLDHAM. Choline as a factor in the elaboration of adrenaline, 696
STEIN, K. F. Sex difference in gonad-stimulating potency of young gonadectomized rats, 424
STEIN, S. I. Experimental studies on the hypophysis cerebri. The effect of vitamin E deficiency in the female albino rat, 441
STEINBERG, A. See Rowntree, L. G., 408, 701
STEINITZ, E. Cachexia of pituitary origin and related conditions, 129
STEINKAMM, E., and W. GIESEN. Note on the question of the follicle hormone effect on blood pressure, 424
STEMMER, W. Treatment of vomiting of pregnancy by means of adrenal cortex (cortin), 247
Sterility, antihormonal, 257
etiology and treatment of, 705
in man treated by gonadotropic hormones, 711
periodic, biologic basis of, 580
produced by hormones, 413, 713
STERN, B., and D. R. GILLIGAN. Effect of hypothyroidism on antidiuretic action of pressor principle of posterior pituitary, 129
STERN, B. See Ernstene, A. C., 597
STERNBERGER, H. R. See Hummel, F. C., 583
STEPPUHN, O. On the metabolic hormone and the insulinogenic substance of the hypophysis, 282
STEVENSON, E. See Thompson, E., 726
STEWART, G. E., R. O. GREEP and O. O. MEYER. Effect of reduced oxygen tension upon formed elements of blood of hypophysectomised animals, 441
STICH, V. See Bergauer, V., 573
STIMMEL, B. F., D. R. MCCULLAGH and V. PICHA. The thyrotropic hormone of the pituitary gland and iodine metabolism, 725
STOTZ, E. H. See Root, H. F., 446
STOUT, A. P. See Cahill, G. F., 570
STOUT, R. E. See Karnosh, L. J., 606
STRANDELL, B. Experiments to isolate the antianemic principle of the liver, 702
STRAUSS, M. See Harrop, G. A., 241
STRAUSS, M. B. See Buell, M. V., 291
STRIECK, F. Diabetes and cirrhosis of the liver, 447
STRONG, L. C. See Gardner, W. U., 416, 705
STUBBE TEGLBJAERG, H. P. Clinical experiments with McQuarrie's pitressin test, 725
STURM, A., and W. SCHONIG. Presence of thyreotropic hormone in non-hypophyseal tissues, 305
STUTINSKY, F. Expansion of erythrophores in Phoxinus laevis by non-hypophyseal products, 409
SUBBAROW, Y., B. M. JACOBSON and C. H. FISKE. A partially purified liver extract therapeutically effective in pernicious anemia, 703
Sucrose tolerance compared with glucose tolerance, 447
Sugar control in diabetes mellitus, 285
estimations, two hourly in diabetes, 598
Sulfur metabolism and adrenalectomy, 695
effect of adrenalin on, 407
effect of insulin on, after splenectomy, 407
and the spleen, 407, 459
SUNTZEFF, V. See Moskop, M., 258
Superovulation and menopause urine, 268
Supraoptico-hypophyseal system, effect of diabetes insipidus on, 433
SURE, B., and K. S. BUCHANAN. Vitamin B and thyroxin, 739
Surgery in toxic goitre, 456
pressoreceptor nervous system in, 603
SUSMAN, W. Adenomata of the pituitary, with special reference to pituitary basophilism of Cushing, 129
SVIRBELY, J. L., and E. C. KENDALL. Vitamin C and the adrenal cortical hormone, 876
SWINGLE, W. W. See Pfiffner, J. J., 245
Sympathectomy and pancreatic diabetes, 288, 731
and Raynaud's disease, 115
Sympathetic denervation, effect of, on ovulation and estrus, 423
stimulation and effect of adrenalin on vascular response, 113
Sympathin, effects of, on iris and nictitating membrane, 113
exhaustibility of, following stimulation, 114
reflexly liberated, 244
physiologic production of, in the liver, 247
Sympathomimetic substances and ultraviolet light, 240
Syphilis, the epiphyses in, 305

TAKASHIMA, R., and S. HARA. Development of the thyroid gland of Japanese, 305
TALBOT, F. R., E. B. WILSON and J. WORCESTER. Standards of basal metabolism of girls (new data) and their use in clinical practice, 703
TANAKA, S. See Ogata, A., 259
TANGL, H., and F. THAN. A hyperglycemic substance from the pancreas, 290
TANG-SŪ. See Kuschinsky, G., 591
TANZI, B. Insulin and the glycolitic system isolated from the heart of the rabbit and the cat, 447
TARR, A. D. See Gersh, I., 718
TAUSK, M. See de Fremery, P., 416
TAYLOR, A. R. See Pfiffner, J. J., 116
TAYLOR, A. P. See Vars, H. M., 247
TAYLOR, H. C., JR. The relation of chronic mastites to certain hormones of the ovary and pituitary and to coincident gynecological lesions, 714
TAYLOR, R. G. See Rand, C. W., 722
TAYLOR, S. G. See Thompson, W. O., 282, 305
TEEM, M. VAN B. The relation of the interstitial cells of the testis to prostatic hypertrophy, 424
TELINDE, R. W., and J. N. BRAWNER. Experiences with amniotin in the treatment of gonococcal vaginitis in children, 424

Temperature effect on calorigenic action of dinitrophenol, 303
TENDICK, F. H. See Dox, A. W., 415
Teratoma testis, diagnosis of, 259
gonadotropic substance in, 253
prolan A in, 250
of pineal, operative removal of, 452
Testes, effect of corpus luteum extract on, 252
effect of gonadotropic hormones on, 719
effect of hypophysectomy on, 717
effect of tumor growth on, in normal rat, 586
effect of light on growth of, 255, 703
estrus-stimulating material in, 119
histology of, as related to prostatic hypertrophy, 424
and hypophysis, 271
influence of castration on prostate, 415
investigation of, in different psychoses, 583
modified by folliculin injections, 716
regeneration dependent on hypophysis, 589
regression following damage to hypophysis, 273
role of eyes in stimulating action of artificial light on, 410
stimulation of by estrogens, 879
stimulation of, by parabiosis, 421
treatment of undescended, 192, 423, 425, 708, 714, 727
Vitamine C in, 254
extract, effect of, on blood sugar, 250
extract, effects of, on comb growth, 417
extract, effect of, on prostate, 420
extract, effect of, on plumage and eye-color of female blackbird, 704
extract and erythrophore expansion, 409
tissue, metabolism of, 120
tumors, and output of gonadotropic hormone, 707
Testosterone, chemical nature of, 412
group, comparative activities of, 414
Testicular development, effect of artificial and natural light on, 409, 577, 578
hormones, assay of water-soluble compounds of, 711
hormones, chemical nature of, 412
hormone, estrogenic action of, 412
hormone preparations, action in male and female rats, 418
implantations in females, 257
treatment in prostatic hypertrophy, 711
Tetany, latent, effects of theelin and theelol in, 421
THADDEA, S. and A. WALY. The action of postpituitary extract on carbohydrate metabolism, 726
THAN, F. See Tangl, H., 290
Theelin, effect of, on duration of estrus, 119
effect of, on plumage and eye-color of blackbird, 406
excretion of, 423
inactive substance in extraction of, 415
in latent tetany, 421
in treatment of acroparesthesia, 417
in treatment of vulvovaginitis, 259
Theelol, activity of, 421
inactive substance in extraction of, 415
isolation of combined form from urine, 413
in latent tetany, 421
THER, L. Is osteogenesis imperfecta an endocrine disease? 118
Therapy, glandular, 121
THOMAS, E. P. See Collins, C. G., 431
THOMAS, W. L. JR. See Hamblen, E. C., 582
THOMAS, R. See Morgan, A. F., 450
THOMPSON, E., E. STEVENSON and F. KROCK. Xanthoma diabeticorum, 726
THOMPSON, G. P. See Uhlenhuth, E., 739
THOMPSON, J. The influence of the intake of calcium on the blood iodine level, 690
THOMPSON, J. H., and J. S. HUXLEY. Retardation of growth in axolotls resulting from parathyroid extract administration, 451
THOMPSON, K. W., and H. CUSHING. Experimental pituitary basophilism, 130
THOMPSON, K. W. See Loeser, A., 126
THOMPSON, P. K. See Thompson, W. O., 282, 305
THOMPSON, W. H. See McQuarrie, I., 731
THOMPSON, W. O., S. G. TAYLOR, P. K. THOMPSON and L. F. N. DICKIE. Calorigenic action of extracts of anterior lobe of pituitary, 282
THOMPSON, W. O., P. K. THOMPSON, S. G. TAYLOR and L. F. N. DICKIE. Oral and duodenal administration of single large doses of pure thyroxine; comparison of calorigenic effects with those of monosodium thyroxine and thyroxine in alkaline solution, 305
THOMSEN, O. A method for demonstrating small quantities of gonadotropic hormone in the urine of normal individuals, 726
Thomsen's disease, thyroid extract in, 301
THOMSON, D. L. See Collip, J. B., 124, 600
THOMSON, D. L. See McEuen, C. S., 275
THOMSON, D. L. See Selye, H., 261, 281
Thrombo-angiitis obliterans, effect of estrogenic substance in, 421
THURSTON, E. W. See Holden, R., 271
Thymectomy, effect of, on growth and development, 408
Thymus after hypophysectomy, 453
and anaesthesia, 453
of castrate rats treated with testicular hormones, 418
decrease in weight after exhaustion, 573
effect of, on uterine activity, 256
elimination of nucleic acid from, after x-ray involution, 452
extract, effect of, on growth and development, 408, 701
extract and erythrophore expansion, 409
origin of, in guinea pigs, 453
Thyrotropic hormone, assay of, in different types of cattle, 122
hormone, effect of, on diuresis and blood pressure, 128
hormone and mineral metabolism, 455
hormone in non-hypophyseal tissues, 305
hormone, temperature effect on secretion of, 592
Thyro-cytotoxin, cretinism due to, 300
Thyroglobulin, metabolic effects of human, 303
Thyroid activity after pituitary treatment, 739
activity during menstruation, 706
activity and iodin metabolism, 734
and adrenal glands, developmental anatomy of, 118
deficiency, effect of, upon skull growth in sheep, 306
deficiency, the epiphyses in, 305
desiccated, and calcium excretion, 736
desiccated, and chronic fluorosis, 460
desiccated, effect on estrus cycle, ovaries and hypophysis in comparison with dinitrophenol, 456
Thyroid disease and blood cholesterol, 297, 406
effect of food and sanitation on, 136
iodin relationships of, 604
and psychoses, 297
treatment of, 609
Thyroid extract and adrenal cortex lesions, 697
change in blood chloride due to, 291
and diuresis, 407
and erythrophore expansion, 409
and exophthalmos, 738
in obesity treatment, 134
relation of dietary fats to action of, 457
in Thomsen's disease, 301
in treatment of cryptorchidism, 708
feeding effect of, on estrus cycle, 294
Thyroid feeding, effect of, on heart size, 304
feeding and moulting in geese, 737
function and blood lipoid, 454
Thyroid gland, action of cortin on hyperactivity of, 240
basic amino acids from, 135
and blood pressure, 458
calorigenic action of, 301
and calorigenic action of adrenalin, 698
carcinoma of, in children, 735
and circulation rate, 457
and conditioned reflexes, 735
cyclic response to excitation and depression, 294
cytological response of, to treatment with anterior hypophysis and potassium iodide, 296
development of, in amia calva, 456
development of, in chick embryo, 606
development of, in frog, 604
development of, in Japanese, 305
development in urodeles, 738
dynamic cytology of, 610
effect of acid extract of anterior hypophysis on, 440
effect of antithyrotropic facter of blood on, 724
effect of cod liver oil on, 455
effect of deficiency of iodin and vitamin A on, 454
effect of hypophysectomy on regeneration of, 298
effect of incomplete extirpation of, 740
effect of injections of ovalbumin on, 268
effect of insanitary condition on, 299
effect of light and darkness on, 299
effect of, on sulfur, 459
effect of vitamins A and C on, 574
and excess iodin, 291

and galactose metabolism, 408
and growth, 733
histological structure and clinical picture in exophthalmos, 739
human fetal, and development of frog larvae, 736
and hypophysis, 301
influence of surviving tissue on metabolism, 300
innervation of, 459
interstitial islets of, in guinea pig, 602
interrelations of, 609
and iodin content of blood, 303
iodin content of, in sterile cattle, 605
ligation of arteries of, in angina pectoris, 608
at the menopause, 460
and mental retardation, 699
and personality, 406
physiology of, 609
and pigmentation, 405
polarity of Golgi apparatus in, 739
relation between iodin content and function of, 608
role of, in carbohydrate metabolism, 297
seasonal changes in, 740
separation of colloid from, by centrifugal force, 458
and sex cycle, 454
significance of colloid vacuoles of, 740
stimulation by pituitary, 126
and susceptibility to poliomyelitic virus, 298
therapeutics of, 299
thyroxine and di-iodo-tyrosine of, in different functional conditions, 734
and ultimobranchial body in fetal calf, 607
and vitamin C content of cerebrospinal fluid and adrenals, 302
Thyroid hormone, action of, on pigmentation in birds, 306
requirements of, in human hypothyroidism, 455
and salt crystallization, 573
Thyroid hyperactivity after ovariectomy, 584
iodin and thyrotropic hormone, 725, 734
substance, effect of, on activity of lipase and catalase in vitro, 297
substance, effect of, on antithyrotropic activity of thyroidectomized sheep's blood, 293
therapy in mongolian idiots, 408
tissue, effect of iodin on growth and metabolism of, 609
Thyroidectomy and anterior pituitary preparations, 276
and the brain, 304
changes in hypophysis after, 283
and dinitrophenol, 303
effect of, on ascorbic acid metabolism, 459
effect of, on estrus cycle, 294
and gonad-stimulating hormones, 436
in heart disease, 135, 454, 736, 737
loss of iodin following, 292
and pituitary storage of mammotropin in male rats, 437
in rabbits, effect on hematopoiesis, 739
Thyroparathyroidectomy and bile-acid production, 451
Thyrostimulin, action of diiodotyrosine and inorganic iodine after, 293
Thyrotoxicosis, impedance angle and basal metabolism, 303
treatment of, 734
Thyrotropic substance, action of, on thyroxin content of blood, 283
effect of, on circulation, 271
elimination of, in urine of menopause, 588
and iodin metabolism, 725, 734
and oxygen consumption, 724
Thyroxin, action co-efficients of effect of, 294
action of, on plants, 295
and adrenal cortex extract, 572
in alkaline solution, effect of, 305
and bile composition, 699
concentration in blood following hypophyseal extract injections, 283
decrease of effect of, by administration of tyrosine, 453
dehydration processes in tissues of animals treated with, 302
duodenal administration of, 305
effect of, on ascorbic acid metabolism, 459
effect of on body temperature of animals with transected spinal cord, 605
effect of, on heat regulation during growth, 298
effect of, on liver amylase, 409
effect of, on liver glycogen, 594
effect of, on metabolism, 460
effect of, on plumage and eye-color, 406, 456, 458
effect of, on reflex excitability, 610
effect of, on serum lipase, 296
effect of, on uterine activity, 256
and hair growth, 738
and metabolism of heart, 455
in normal and pathological thyroid glands, 734
oral administration of, 305
prenatal secretion of, 293
sensitivity to, 733
and tissue metabolism, 292
and vitamin C, 738
TIMPARELLI, A. See Root, S., 246
Tissue culture of hypophysis, 269
cultures, survival and increase of epinephrin in, of adrenal glands from chick embryos, 244
enzymes in hyperthyroidism, 453
metabolism of heart, 455
metabolism in hyperthyroidism, 453
metabolism after adrenalectomy, 571
metabolism and thyroxin, 304
respiration and thyroid, 300
TITELBAUM, S. See Kleitman, N., 735
TOBIN, E. See Gaunt, R. C., 404
TODD, T. W., and R. E. WHARTON. The effect of thyroid deficiency upon skull growth in the sheep, 306
TOMILIN, M. I. Length of gestation period and menstrual cycle in the chimpanzee, 424
TOMORUG, E. See Parhon, C. I., 127, 450
TOPSTEIN, R. See Serejske, M., 304
TORE, D. See Cioglia, L., 578, 586
TOURNADE, A., and A. CURTILLET. Observations on suprarenal-jugular venous anastomosis, 696
TRANCU-RAINER, M., and O. VLADUTIU. The presence of the sex hormone and the indifferent gonadotropic hormone of the anterior lobe of the hypophysis in the urine and saliva of a giant, 441
TRESCHER, J. H. See Harrop, G. A., 114
Tryptophane in normal and pathological thyroid glands, 734
TSCHERNING, K. See Butenandt, A., 411, 578
TSCHERNJAK, F. S. See Yakobson, L. A., 306
TSCHOPP, E. The physiological activity of synthetic male sex hormone, 714
TSURIGIRO, K. See Itho, M., 580
Tuber cinerea, damage to, and weight and histology of adrenals, 242
Tuber cinereum and hypophysis function, 721
Tuberal lesions, pituitary infarcts following, 592
Tuberculosis and Addison's disease, 116
and parathyroid hormone, 449
pituitary hyperfunction in, 591
TUM SUDEN, C. See Wyman, L. C., 116
Tumor growth in castrate rats of various ages, 586
in senile rats, 586
influenced by insulin, 446
inhibited after hypophysectomy, 592
Tumors, adrenal cortical, 570
and hypophyseal hormones, 441
theca cell, 254
Tungstic acid method for extraction of urinary estrogenic substance, 415
TURCATTI, E. S. See Lewis, J. T., 288, 731
TURNER, H. H. Anterior-pituitary dwarfism, 441
TURNER, H. H. The epilepsies associated with endocrine disorders, 118
TUZIOKA, S. Effect of thyroparathyroidectomy on bile-acid production in dogs, 451
TWEEDY, W. R. See Roberts, R. G., 451
Tyrosine, ameliorating effect of, in experimental hyperthyroidism, 453
in normal and pathological thyroid glands, 734
variations of, in inactivated insulin, 730
TYSON, T. L. See Gutman, A. B., 601

UENO, F. See Ito, M. S., 708, 709
UHLENHUTH, E., S. S. SCHWARTZBACH and G. P. THOMPSON. Physiology of the thyreoactivator in amphibia. Structural changes in the thyroids of salamanders treated with anterior lobe, 739
UHLENHUTH, E. See Schwartzbach, S., 724
UHLENHUTH, E. The Golgi apparatus in the thyroid gland of amphibians in its relation to excretion polarity, 739
UNIK, V. See Zavadovsky, B., 278, 426
Ureters, effect of ligature on water absorption by skin, 277
Urinary casts and sediment in hyperparathyroidism, 447
calculi and hyperparathyroidism, 448
Urine of cancer patients, principle in, acting on adrenal cortex, 239
in diabetes mellitus, 285
electrolytes and parathyroid extract, 448

estrin in female, 251
evidence of male hormone in, 254
excretion of gonad-stimulating factor in, after estrin injections in menopause, 434
excretion of gonadotropic hormone in, and relation to menstrual cycle, 438
extraction of estrogenic substance from, 415
from normal children, hypophysis hormone in, 434
procedure for quantitative extraction of sex hormones from, 416
Urogenital tract of male monkey, effect of estrin on, 425
Uterine bleeding (cyclical) in spider monkey, 417
bleeding, dysfunctional, 699
bleeding, functional origin of excessive, 715
contractions, effect of progestin and estrogenic substance on, 581
contraction inhibited by corpus luteum hormone, 581
growth, studies on, 420
hypoplasia, use of progestin in, 703
muscle, activity of, modified by hormones, 256
reaction in vivo and in vitro, 581
reaction to estrin and to oxytocin, 581
Uterus, action of extract of corpus luteum on, 258
effect of estrin on, 415, 581, 711, 713
effect of total ablation of, on ovary, 703
failure of endocrine products to control bleeding, 582
of prolan (A. P. L.) treated infantile rats, 591
reaction to placenta extract, 251
sensitivity of, to corpus luteum and pituitrin, 259

Vagina of prolan (A. P. L.) treated infantile rats, 591
Vaginal mucification, production of, by folliculin, 251
Vaginitis, amniotin in treatment of, 119
juvenile gonococcus, treated with theelin, 260
senile, treatment of, with ovarian follicular hormone, 414
VAGUE, J. See Olmer, D., 732
VALLESI, E. See Falaschini, A., 605
VAN BOGAERT, A. Effect of hypophyseal extracts on the diencephalon and on arterial tension, 726
VAN DER SCHUEREN, G. Inhibiting action of placenta extract on a transplantable malignant epithelioma of the rabbit, 425
VAN WAGENEN, G. The effects of oestrin on the urogenital tract of the male monkey, 425
VAN WAGENEN, G. See Deming, C. L., 251, 415
VAN WEERING, J. Influence of menformone of the epithelium of the neck of the uterus, 425
VAN WINKLE, W. JR. See Luck, J. M., 244
Vasopressin content in guinea pig hypophysis, 724
VEBER, M. P., and E. K. ELENEVSKAYA. Relationship between clinical picture and histologic structure of thyroid in exophthalmic goiter, 739
VENNESLAND, B. See Holt, H., 707
VERZAR, F., and L. LASZT. Inhibition of absorption after the extirpation of the adrenals, 696
VERZAR, F. See Laszt, L., 693
VICTOR, J., and D. H. ANDERSEN. The effects of oestrus and spaying on pituitary metabolism, 726
VICTOR, J., D. H. ANDERSEN and M. R. PREST. Changes in tissue metabolism in oestrual, dioestrual and spayed rats, 715
Vitamin C and thyroxin, 738
VOELKER, C. H. Therapy of the endocrinopathic dyslogia in cretinism, 740
VOLKOVISSKAJA, C. See Raspopova, N. A., 737
VOLOBUIEFF, P. See Raspopova, N. A., 737
VON LUCADOU, W. The adrenals in hypertension, 693
VON TYUKODY, F. See Mansfield, G., 608
VARS, J. M., A. P. TAYLOR and J. J. PFIFFNER. Extraction studies on the adrenal cortical hormone. Yield from glands of various species, 247
VARS, H. M. See Pfiffner, J. J., 116, 245
Vasopressin, influence of, on cardiovascular system of animals, 281
liver and kidney lesions after injections of, 281
VESA, A. The use of two hourly blood and urine sugar estimations in diabetes, 598
VESTERDAL-JORGENSEN, J. See Secher, K., 304
VETTER, H. See Kuhn, R., 407
VILLAGRAN, G. See Lipschütz, A., 593
VILLELA, E. See Lacassagne, A., 256
VILTER, V. The action of the thyroid hormone on pigmentation in birds, 306
VINALS, E. Augmentation of gonadotropic action of pregnancy urine by the epiphysis, 452
VINALS, E. See Lipschütz, A., 120, 256, 274
Viosterol and parathyroid extract, 450
Visual disturbances in diabetes, 446
Vitamin A, effect of, on metabolism after thyroxin, 460
-deficiency and castration, 257
deficiency, effect of, on thyroid, 454
deficiency and estrus, 420
influence of, on experimental hyperthyroidism, 451
Vitamins A and C, effects of, on endocrine glands, 574
A, C, D, influence of on thyroid, 604
Vitamin C in Addison's disease, 115
distribution in hypophysis, 269
metabolism, affected by thyroid hormone, 459
Vitamin D thyrotropic action of, 295
Vitamin E, effect of deficiency of, 441
Vitamins, role of, in maintenance of depancreatized dogs, 284
VIVALDI, T. See Lipschütz, A., 274
VLADUTIU, O. See Trancu-Rainer, M., 441
VOEGTLIN, W. L., H. GREENGARD and A. C. IVY. The response of the canine and human pancreas to secretin, 132
VOLK, M. C. See Gilligan, D. R., 135
VON BERGMANN, G. Leanness and tendency toward emaciation, 264
VON GIERKE'S disease, metabolic studies in, 443
Voss, H. E. See Loewe, S., 419
VOTQUENNE, M. Contribution to the study of humoral antagonism in the rat ovary; the differing thresholds for the anti-luteinizing effects of folliculin, 122
Vulvovaginitis, theelin therapy of, 259

WACHSTEIN, M. Two cases of myxedema treated with thyrotropic hormone, 740
WADE, N. J., and E. A. DOISY. Cornification of vaginal epithelium of ovariectomized rats produced by smearing, 715
WAGENER, H. P., T. J. S. DRY and R. M. WILDER. Retinitis in diabetes, 290
WAGONER, G. Clinical treatment of certain bone diseases caused by hyperfunction of the parathyroid glands, 134
WAHLBERG, J. Grave asthenia due to pituitary disorder, 283
WAITE, J. H., and W. P. BEETHAM. The visual mechanism in diabetes mellitis. (A comparative study of 2002 diabetics and 457 non-diabetics for control), 598
Walker rat tumor, growth of, 275
WALLACE, H. L. See Graham, J. M., 456
WALSH, J. A. See Aldrich, C. A., 602
WALTERS, W., R. M. WILDER and E. J. KEPLER. The suprarenal cortical syndrome with presentation of ten cases, 696
WALTHER, P. See Lévy-Solal, E., 273
WALY, A. See Thaddea, S., 726
WARREN, F. L. See Cook, J. W., 413
WARREN, S., and J. R. E. MORGAN. The parathyroid glands. A histologic study of parathyroid adenoma, 451
Water absorption, effect of hypophysectomy on, 277
economy and sexual functions, 428
exchange, action of hypophysis on, 279
metabolism after damage to infundibulo-tuberal region, 277
metabolism, effect of pituitary on, 728
WATSON, M. C. Observations on the treatment of dysmenorrhoea with the placental extract 'Emmenin,' 715
WAYBURN, E. Complete insulin resistance in diabetes, 290
WEATHERBY, J. H. See Hulpieu, H. R., 590
WEBSTER, B. Effect of anterior pituitary-like principle from the urine of pregnancy on undescended testes in man, 425
WEBSTER, B. See Freedman, B., 294
WECHSLER, H. F. See Packard, M., 694
WEINER, H. A. So-called atrophy of the adrenal cortex, 876
WEIL, A. The phospholipids of the brain, kidneys and heart of white rats in experimental hyperthyroidism, 691
WEIS, M. Histological modifications of the hypophysis of guinea pigs during pregnancy and after parturition, 283
WEIS, M. See Florentin, P., 268, 285
WEISMAN, A. I. See Kleiner, I. S., 710
WEINSTEIN, A. See Harrop, G. A., 114
WELLER, G. See Binet, L., 239
WELLER, G. L., JR. Adrenal insufficiency resulting

from partial or total atrophy of the adrenal glands, 697
WELLS, W. M. See Markee, J. E., 420
WENNER, W. F., and A. J. CONE. Suprarenal Cortex extract in pyogenic infections, 247
WERNER, A. A., D. KELLING, D. ELLERSIECK and G. A. JOHNS. Effect of gonadotropic extract of pituitary in cryptorchidism, 727
WEST, R. Studies in neurologic mechanism of parathyroid tetany, 452
WHARTON, R. E. See Todd, T. W., 306
WHITE, A., and W. G. GORDON. Basic amino acids yielded by thyroglobulin, 135
WHITE, J. C. See Smithwick, R. H., 115
WHITE, P. See Joslin, E. P., 599
WHITE, P. See Marble, A., 289
WHITE, P. See Root, H. F., 446
WHITEHEAD, R. W., and E. E. MCNIEL. The therapeutic effects of estrogenic hormone preparations in certain cases of idiopathic ep :psy and in migraine, 425
WHITEHEAD, R. W. See Fox, C. A., 240
WHITELAW, G. P., and J. C. SNYDER. The physiological production of sympathin in the liver, 247
WHITTEN, M. B. Hyperthyroidism complicated by heart disease, 306
WIDMANN, E. See Schneider, E., 451
WILDER, R. L. A case of hepatonephromegalia glycogenica—von Gierke's glycogen storage disease, 728
WILDER, R. M. See Wagener, H. P., 290
WILDER, R. M. See Sprague, R. G., 733
WILDER, R. M. See Walters, W., 696
WILDSTRÖM, G. On the biological assay of adrenal cortical preparations using white rats and mice, 697
WILKINS, W. E., J. A. CALHOUN, C. PILCHER and E. M. REGEN. The influence of pituitary growth hormone on the phosphate activity of bone and kidney, 283
WILLIAMS, G. H. See Karnosh, L. J., 297
WILLIAMS, P. C. See Dodds, E. C., 432
WILSON, A. T. See Robertson, J. D., 303
WILSON, E. B. See Talbot, F. R., 703
WILSON, H. C. Some observations on the effect of drugs on the ear vessels of the unanaesthetized rabbit as seen in the "preformed-tissue" chamber, 703
WILSON, L., and R. KURZROK. Excessive uterine bleeding of functional origin, 715
WILSON, L. See Kurzrok, R., 418
WINTER, E. W. Suprarenal cortex and female genital apparatus, 247
WINTERS, L. M. See Green, W. W., 417
WINTERSTEINER, O., and J. J. PFIFFNER. Chemical studies on the adrenal cortex. Isolation of several physiological inactive crystalline compounds from active extracts, 248
WINTERSTEINER, O. See Pfiffner, J. J., 245
WITHERSPOON, J. T. The estrogenic, carcinogenic, and anterior pituitary growth principles, and their clinical relation to benign and malignant tumors, 441
WITHERSPOON, J. T. The estrogenic principle, the common etiological factor of endometrial hyperplasia, uterine fibroids and endomitriomas, 426
WITSCHI, E., and C. A. PFEIFFER. The hormonal control of oestrus, ovulation and mating in the female rat, 442
WITSCHI, E. See Du Shane, G. P., 432
WITTENBOURG, W., and J. PORKHOVNIK. Treatment of functional disturbances of menstruation in young women by light doses of x-ray applied to the ovaries and hypophysis, 715
WODSTRUP, I. See Hagedorn, H. C., 444
WOLFE, J. M. Morphologic and quantitative reaction of anterior pituitaries of castrated female rats to oestrin injections, 728
WOLFE, J. M. Reaction of anterior pituitaries of mature female rats to injections of large amounts of oestrin, 728
WOLFE, J. M. Reaction of the anterior pituitaries of mature female rats to prolonged injection of pregnancy urine extracts, 442
WOLFE, J. M. Reaction of the ovaries of mature female rats to injections of oestrin, 716
WOLFE, J. M. See Mason, K. E., 257
WOLFF, E. Interpretation of results obtained with synthetic androsterone injected into chick embryos, 716
WOLFF, E., and A. GINGLINGER. The structure of gonads of different intersex types following injections of male chick embryos with folliculin, 716
WOLFF, H. G. See Shorr, E., 305
WOOD, F. C. See Elsom, K. A., 448
WOODS, O. R. See Gustus, E. L., 705
WORCESTER, J. See Talbot, F. R., 703
WRIGHT, L. M. See Freedman, B., 294
WYLIE, H. B. See Schmulovitz, M. J., 423
WYMAN, L. C., and C. TUM SUDEN. Differential depression of vasomotor mechanisms by adrenin, 116
WYMAN, L. C., and C. TUM SUDEN. The distribution of adrenergic vasodilators in the rat, 877

X-rays, elimination of nucleic acid from thymus after radiation with, 452
treatment of ovaries and hypophysis, for functional disturbances of menstruation, 715

YANAGI, K. The effect of posterior pituitary preparations upon the colloid osmotic pressure of serum protein, water and mineral metabolism of dogs, 728
YAKOBSON, L. A., and F. S. TSCHERNJAK. The clinical significance of blood iodine levels in thyroid disorders, 306
YOUNG, H. H. Abnormalities and plastic surgery of the lower urogenital tract, 716

ZAHARESCO-KARAMAN, I. PORUMBARA and A. S. FOTIN. Coefficient of growth of rat seminal vesicles as a biological test of pregnancy, 426
ZAHL, P. A. Cytological changes in frog pituitary considered in reference to sexual periodicity, 442
ZALESKY, M. Effects of prepuberal gonadectomy on the adrenal gland of the guinea pig, 877
ZALESKY, M. A study of the seasonal changes in the thyroid gland of the thirteen-lined ground squirrel, 740
ZAVADOVSKY, B. M., G. S. ASIMOFF, L. LIPTCHINA and V. J. UNIK. Effect of hormones of sex-cycle on egg-production in hens, 426
ZAVADOVSKY, B., G. ASIMOFF, L. LIPTCHINA and V. UNIK. Influence of prolan on egg-production, 426
ZAVADOVSKY, B., G. ASIMOFF, L. LIPTCHINA and V. UNIK. Effect of a total injection of prolan and folliculin on egg-production in hens, 728
ZECKWER, I. T., L. W. DAVISON, T. B. KELLER and C. S. LIVINGOOD. The pituitary in experimental cretinism. Structural changes in the pituitaries of thyroidectomized rats, 283
ZIMMERMAN, H. M. See Lawrence, J. H., 593
ZIMMERMAN, L. M. See Soskin, S., 440
Zinc salts and insulin, 290
ZLABEK, Z. See Bergauer, V., 573
ZONDEK, B. The inhibitory effect of the follicular hormone on the anterior lobe of the pituitary gland, 427
ZONDEK, B. Tumor of the pituitary induced with follicular hormone, 729
ZONDEK, H. The diseases of the endocrine glands, 237
ZUCKERMAN, S. The effect of sex hormones on the prostate of monkeys, 427
ZUNZ, E., and J. LA BARRE. Action of anterior pituitary thyreotropic substance on the thyroxin content of blood, 283
ZUNZ, E., and J. LA BARRE. Effect of cortin on the secretion of adrenalin, 697
ZWEMER, R. L. A study of adrenal cortex morphology, 697

THIS NUMBER, WITH INDEX, COMPLETES VOLUME 20

NOV 2 0 1936
MEDICAL LIBRARY

ENDOCRINOLOGY

THE BULLETIN OF
THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

VOLUME 20 NOVEMBER, 1936 NUMBER 6

CONTENTS

The Human Corpus Luteum and Progestin, Studies II. *J. P. Pratt, E. C. Hamblen, O. Kamm and D. A. McGinty* 741
The Effect of Estrogenic Substances upon the Pituitary, Adrenals and Ovaries. *Eugene T. Ellison and John C. Burch* 746
The Time Element in the Pituitary-Ovarian Response to Large Doses of the Estrogenic Hormone. *Charles Mazer, S. Leon Israel and Bernard J. Alpers* 753
The Effect of Interruption of the Supraoptico-Hypophyseal Tracts on the Antidiuretic, Pressor and Oxytocic Activity of the Posterior Lobe of the Hypophysis. *C. Fisher and W. R. Ingram* 762
The Endometrium in "Endometrial Hyperplasia" after Therapy. *E. C. Hamblen* 769
Treatment of Sexual Underdevelopment in the Human Male with the Anterior-Pituitary-Like Hormone (A.P.L.) of Pregnancy Urine. *Daniel L. Sexton* 781
Visceral Temperatures in the Intact and Unanaesthetized Animal. II. The Uterus of the Rat. *James B. Hamilton* 788
Extracts Containing Cortin. *Frank A. Hartman and W. D. Pohle* 795
The Genesis of Thyroid Protein: Clinical Assays of Artificial Thyroid Protein in Human Myxedema. *W. T. Salter and J. Lerman* 801
The Influence of the Intake of Calcium on the Blood Iodine Level. *Juanita Thompson* 809
Subclinical Hypothyroidism in Children. *Matthew Molitch and Sam Poliakoff* 816
Nitrogen and Creatine Metabolism in Relation to Environmental Temperature and Thyroid Function. *M. Bodansky and Virginia B. Duff* 822
The Significance of Electrical Impedance Measurements on the Human Body. *J. W. Horton and Saul Hertz* 831

Case Reports
Thyroid Dysfunction in Hemochromatosis. *M. Norman Orgel and David Barr* 839
Fugitive Acromegaly. Acromegaly Followed by Pituitary Cachexia. Treatment with an Alkaline Extract of the Anterior Pituitary. *E. Kost Shelton, Lyman A. Cavanaugh and Paul R. Patek* 846
Hypertrophy of the Testes with Symptoms of Hyperorchidism. *J. K. Fancher* 852
The Treatment of Pituitary Infantilism with Anterior Pituitary Extract. *Max M. Goldberg* 854
Pituitary Infantilism with Diabetes Mellitus. *Daniel L. Sexton and Fritz Neuhoff* 856

Clinical and Laboratory Notes
A Simple Method of Hypophysectomy in the Dog. *Richard J. Bennett, Jr.* 860
On the Evaluation of the Potency of Estrogenic Substances. *S. C. Freed and S. Soskin* 863
Further Investigation of the Hormone Content of Saliva Using the Female Bitterling Test. *Abner I. Weisman* 864
Dating Endocrine Substances: A Plea for Fresh Products. *Israel Bram* 866
Current Endocrine Literature 867

Published Six Times a Year by The Association for the Study of Internal Secretions

Annual Subscription, $6.00 *Single Copy, $1.25*

Complete YOUR FILES

Back Issues of ENDOCRINOLOGY

at half price

For a limited time only we offer surplus copies of certain back issues of ENDOCRINOLOGY at 50 cents each, postpaid.

The following numbers are included in this offer:

Vol. 3, 1919, all 4 nos.; Vol. 4, nos. 2 and 3; Vol. 5, nos. 1, 2, 3, 4, 6; Vol. 6, all 6 nos.; Vol. 7, nos. 1, 2, 3, 5; Vol. 8, nos. 1, 2, 3, 4, 6; Vol. 9, nos. 1, 2, 3, 4, 5; Vol. 10, nos. 1, 2, 3, 4, 6; Vols. 11, 12, 13, 14, 15, all 6 nos. of each; Vol. 16, nos. 2, 3, 6; Vol. 17, 1933, nos. 2, 3, 4, 5, 6.

Additional discount of 10% allowed on orders amounting to $20 or more.

Copies of most other back issues are available at regular prices.

ORDER FORM

ENDOCRINOLOGY

1930 Wilshire Blvd., Room 1214

Los Angeles, Calif.

Please send, carriage prepaid, the following back numbers of ENDOCRINOLOGY. Remittance to cover, at 50 cents per copy, is enclosed.

Vols. and nos. .....

Vols. and nos. .....

Vols. and nos. .....

Name .....

Address .....

NOTICE TO CONTRIBUTORS

ENDOCRINOLOGY, the official publication of The Association for the Study of Internal Secretions, comprises original articles, case reports, occasional editorial articles, news items, book reviews and abstracts of current literature in experimental and clinical endocrine biology and medicine.

Original articles are accepted for publication only with the understanding that they are contributed *exclusively to this journal.* Preliminary notices will not be accepted.

An abstract of less than 250 words or a copy of the summary of the article typewritten on a separate sheet with the title and author's name must accompany the manuscript. This abstract will be published in the abstract section of the journal in advance of the appearance of the complete article.

Manuscripts should be typewritten in double spacing with wide margins on one side of paper 8½ x 11 inches and should be packed flat. Tables, case histories and other subsidiary matter usually set in smaller type than the text should be typewritten on separate sheets and placed with the text in correct sequence. Footnotes and legends for figures should be typewritten on separate sheets at the end of the text copy. Footnotes should be used sparingly. Case histories and protocols should be written in clear, concise statements in the past tense and not in incomplete sentences and disjointed phrases.

Citations of literature should be numbered serially in the text. References to cited papers should not be given in the text but should be arranged in a list at the end of the paper in the order of citation and preceded by the corresponding serial number. The reference should conform to the practice of the Quarterly Cumulative Index Medicus: author's name, journal, volume (in Arabic), initial page and year. Authors are urged to verify personally the accuracy of the references, using only the original sources.

Each article should conclude with a summary of usually not more than 250 words, suited to the needs of abstract journals. This summary should be intelligible without reference to the body of the article. The factual evidence should be stated quantitatively.

A certain number of illustrations and tables will be allowed without charge. Arrangements must be made with the Editor for excess illustrations and tables.

All illustrative material should be submitted in finished form so as to admit of photographic reproduction without retouching, redrawing, labelling or the setting of marginal type.

Original drawings, not photographs of drawings, should be sent. These should be made on white or blue lined heavy paper or bristol board and should be arranged to conserve vertical space.

When photographs are used for half-tone reproductions glossy prints with as sharp contrast as possible should be submitted unmounted. All unnecessary material should be trimmed away. Actual magnifications of photomicrographs should be given. In grouping illustrations it should be borne in mind that text figures after reduction cannot exceed the dimensions of the printed matter on the page, 4.66 x 7.75 inches. The preparation, arrangement and trimming of illustrations and the arrangement of tabular data so as to conserve vertical space on the page is especially urged. The approximate position of text figures should be indicated on the manuscript. The author should place his full address at the top of the first page of the manuscript, and his name on the back of each photograph or drawing.

Manuscripts, correspondence relating to the editorial management and books for review should be sent by mail or by prepaid express to the Editor, Dr. R. G. Hoskins, 25 Shattuck St., Boston, Massachusetts.

Galley proofs and engraver's proofs are sent to the author.

Reprints: A price list and order blank for reprints will be sent with the galley proofs.